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(54) Title: RIBAVIRIN-INTERFERON ALFA COMBINATION THERAPY FOR ERADICATING DETECTABLE HCV-RNA IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION			
<p style="text-align: center;">(I)</p>			
(57) Abstract			
<p>Ribavirin derivatives represented by formula (I) wherein at least one of R<sup>2</sup>, R<sup>3</sup> or R<sup>5</sup> is a straight or branched chain polyalkylene oxide polymer conjugate, and pharmaceutical compositions containing them as well as their use to treat patients having susceptible viral infections, alone and in combination with a therapeutically effective amount of interferon-alpha are disclosed.</p>			

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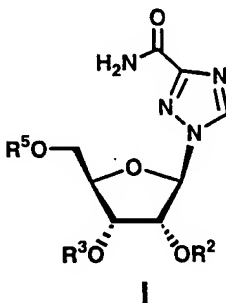
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**RIBAVIRIN-INTERFERON ALFA COMBINATION THERAPY  
FOR ERADICATING DETECTABLE HCV-RNA  
IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION**

**BACKGROUND OF THE INVENTION**

The present invention relates to ribavirin derivatives represented by formula I



wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and pharmaceutical compositions containing them as well as their use to treat patients having susceptible viral infections, alone and in combination with a therapeutically effective amount of interferon-alpha.

Chronic infection with hepatitis C virus is an insidious and slow-progressing disease having a significant impact on the quality of life. It can eventually result in cirrhosis of the liver, decompensated liver disease and/or hepatocellular carcinoma.

Combination treatment with interferon alfa-2b and ribavirin of patients with chronic hepatitis C is disclosed by Reichard et al. (The Lancet **1998**; 351;83-87; and T. Poynard et al. (The Lancet, **1998**, Vol. 352, Oct. 31, p 1426-1432). See also J. G. McHutchinson et al. (N. Engl. J. Med., **1998**, 339:1485-1492); and G. L. Davis et al. (N. Engl. J. Med., **1998**, 339:1493-1499). However, this combination therapy is not always effective due to side effects associated ribavirin such as ribavirin-related hemolysis, and anemia.

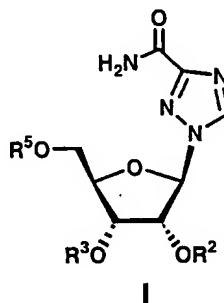


There is a definite need for more potent, safer ribavirin derivatives having fewer side effects for use as monotherapy or in combination with antiviral agents, e.g., interferon-alpha, to treat patients having susceptible viral infections, e.g., chronic hepatitis C infections, in a long-term, effective manner.

5

### SUMMARY OF THE INVENTION

The present invention provides a compound represented by formula I



10

wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^2$ ,  $R^3$  or  $R^5$  is  
 15 H,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$  and wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is not H; wherein  $R^6$  is H, alkyl, alkanoyl, aryl, heterocyclic, cycloalkyl,  $NR^{7a}R^{7b}$ , alkenyl, or alkynyl;  
 or  $R^6$  is alkyl, alkanoyl, alkenyl or alkynyl substituted by halo, phenyl, cycloalkyl,  
 20  $NR^{7a}R^{7b}$ , hydroxy, or alkoxy;

or  $R^6$  is aryl substituted by phenyl; halo, CN,  $NO_2$ , OH,  $R^{18}$ ,  $CF_3$ , SH,  $SR^{7a}$ ,  $SOR^{7a}$ ,  $SO_2R^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $CO_2H$ ,  $CO_2^-$ ,  $OR^{7a}$ ,  $O^-M^+$  or  $S^-M^+$   
 wherein  $M^+$  is an alkali metal,

25

W is O,  $NR^{18}$  or S;



$R^{7a}$  is H, alkyl, alkanoyl, or aryl; or  $R^{7a}$  is alkyl, alkanoyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

and  $R^{7b}$  is H, alkyl or aryl or  $R^{7b}$  is alkyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

5

or  $R^{7a}$  and  $R^{7b}$  taken together with N and one of  $CHR^{7a}$ ,  $NR^{7a}$ , O, S, SO or  $SO_2$  form a five-, six- or seven- membered ring;

$R^{17}$  is H,  $OR^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $R^6-(W)_xCO-$ ,  $R^6-(W)_xCS-$ ,  $R^6-(W)_xC=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_xPO(OH)-$  or  $HO-SO_2-$ ;

10

$R^{18}$  is H, alkanoyl or alkyl;

and  $x = 0$  or  $1$ ;

or a pharmaceutically acceptable salt thereof.

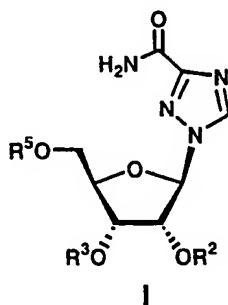
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The present invention provides a method of treating patients having a susceptible viral infection, such as a chronic hepatitis C infection

20

The present invention provides a method of treating patients having comprising administering a therapeutically effective amount of a ribavirin derivative of formula I and a therapeutically effective amount of interferon-alpha for a time period sufficient to eradicate detectable HCV-RNA at the end of said period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin derivative is represented by formula I:

25

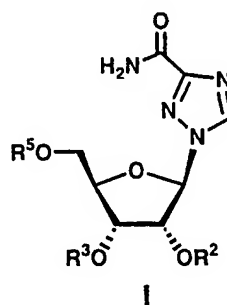


The present invention also provides a method of treating patients having chronic hepatitis C infection comprising administering a therapeutically effective amount of a



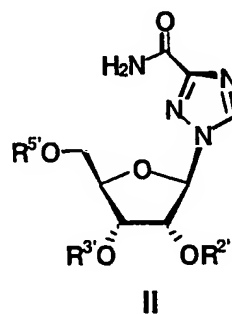
ribavirin derivative of formula I and a therapeutically effective amount of interferon-alpha for a time period of at least 20 to 50 weeks to eradicate detectable HCV-RNA at the end of said 20 to 50 week period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin

5 derivative is represented by the formula I:



10

The present invention provides a compound represented by formula II



15 wherein at least one of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a natural or unnatural  $\alpha$ -amino acid residue.

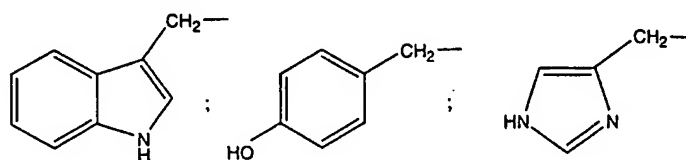
In a preferred embodiment, the natural or unnatural  $\alpha$ -amino acid residues for the compounds of formula II are represented by the formulas

20



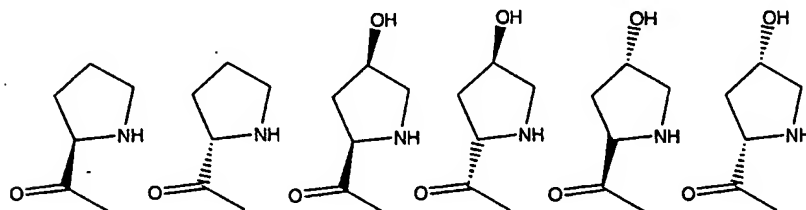


Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



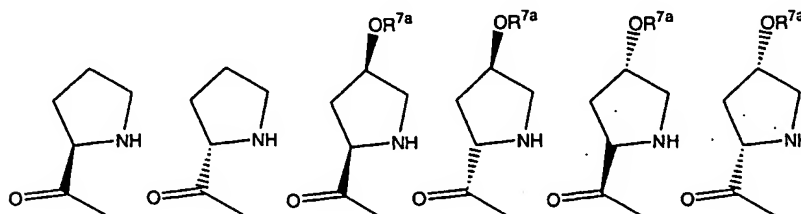
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof;

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof;

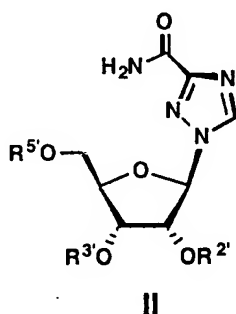
or Y taken together with the  $\alpha$  carbon and N form



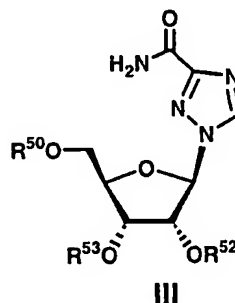
or a pharmaceutically acceptable salt thereof;



In another embodiment, the present invention relates to a method of treating patients having chronic hepatitis C infection comprising administering a therapeutically effective amount of a ribavirin derivative of formula II and a therapeutically effective amount of interferon-alpha for a time period sufficient to eradicate detectable HCV-RNA at the end of said period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin derivative is represented by formula II



The present invention also provides a compound represented by formula III



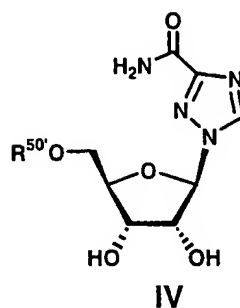
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wherein at least one of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  is a straight or branched chain polyalkylene oxide polymer conjugate, and the remaining two of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  are independently H or a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof.

20 In a preferred embodiment,  $R^{52}$  and  $R^{53}$  in the compounds of Formula III are each H.



The present invention further provides a compound represented by the formula IV



5        wherein  $R^{50'}$  is a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof.

10        The present invention also provides pharmaceutical compositions for treating susceptible viral infections comprising a compound of formula IV and at least one pharmaceutically acceptable carrier.

15        The present invention also provides a method of treating a patient with a susceptible viral infection which comprises administering to said patient an effective amount of a compound of formula IV

20        The present invention also provides a method of treating a patient infected with chronic hepatitis C which comprises administering to said patient an effective amount of a compound of formula IV in association with an effective amount of an interferon alfa for a time sufficient to eradicate detectable HCV-RNA levels.

#### DETAILED DESCRIPTION

25        The term "alkyl" as used herein means straight and branched carbon chains of one to twenty carbons, preferably one to six carbons, and more preferably one to three carbons.



The term "alkenyl" as used herein means straight and branched chain alkyl groups containing at least one carbon-carbon double bond and two to twenty carbons, preferably two to eight carbons.

5       The term "alkynyl" as used herein means straight and branched chain alkyl groups containing at least one carbon-carbon triple bond and two to twenty carbons, and preferably two to six carbons containing at least one carbon-carbon triple bond.

10       The term "cycloalkyl" as used herein means carbocyclic rings of three to twelve carbons, preferably three to seven carbons, and more preferably three to six carbons optionally substituted by one double bond.

15       The term "alkanoyl" as used herein means straight and branched chain alkanoyl groups of one to twenty carbons, preferably two to twelve, more preferably two to ten and most preferably two to six carbons.

20       The term "alkenoyl" as used herein means straight and branched chain alkenoyl groups of one to twenty carbons containing at least one carbon-carbon double bond, preferably two to twelve, or more preferably two to ten and most preferably two to six carbons containing at least one carbon-carbon double bond.

The term "halo" as used herein means fluorine, chlorine or bromine, preferably fluorine or chlorine.

25       The term "alkynoyl" as used herein means straight and branched chain alkenoyl groups of one to twenty carbons containing at least one carbon-carbon triple bond, preferably two to twelve, or more preferably two to ten and most preferably two to six carbons containing at least one carbon-carbon triple bond.

30       The term "alkoxy" as used herein means straight and branched chain alkyl groups containing one bond to oxygen at the one carbon and one to ten carbons. Typically suitable alkoxy includes methoxy, ethoxy and tert-butoxy.

35       The term "aryl" as used herein (including the aryl portion of aryloxy and aralkyl, e.g., benzyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), or is a polycyclic aromatic containing one or more heteroatoms, e.g., N or S such as quinoyl, isoquinoyl, with all

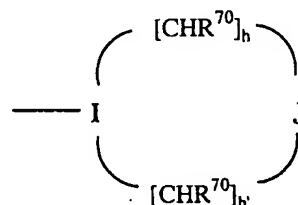


available substitutable carbon atoms of the carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halogen, alkyl, hydroxy, alkoxy, CN, phenoxy,  $\text{CF}_3$ , amino, alkylamino, dialkylamino, SH,  $\text{S}^+ \text{M}^+$  or  $-\text{NO}_2$ ; and the term " $\text{M}^+$ " represents an alkali metal cation such as  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Li}^+$ .

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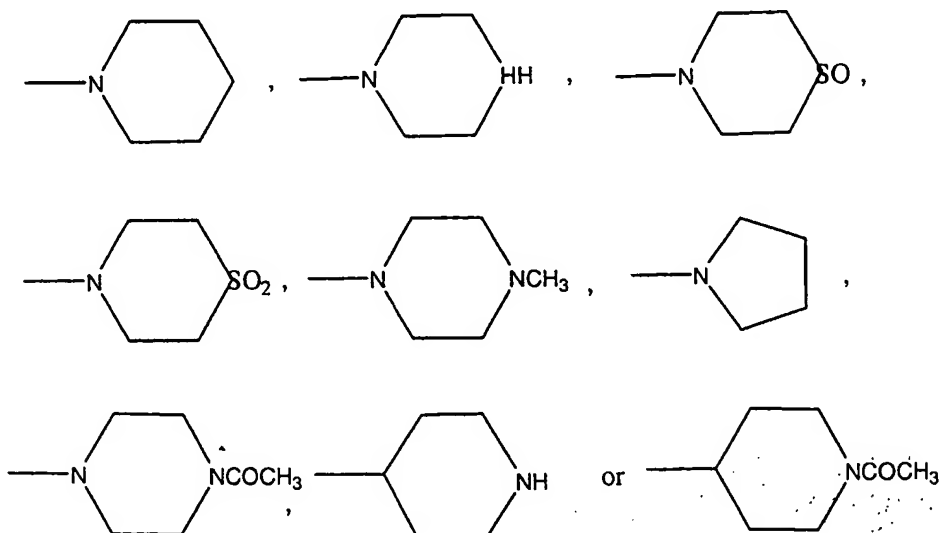
The term "arylalkyl" as used herein means an alkyl group substituted by an aryl group.

10 The term "heterocyclic" as used herein means a cyclic group represented by the formula;



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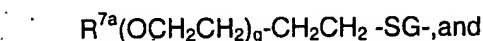
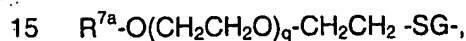
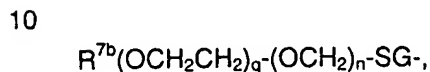
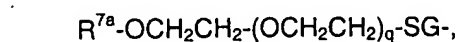
wherein J is  $-\text{CHR}^{70}$ -,  $-\text{O}-$ ,  $-\text{NR}^{70}$ -,  $-\text{S}-$ ,  $-\text{SO}-$  or  $-\text{SO}_2-$ , and I is  $-\text{CR}^{70}$  or  $-\text{N}-$ ; and  $\text{R}^{70}$  is H, alkyl or aryl; and h and h' are independently 1 to 4 and the sum of h + h' is 2, 3, 4 or 5. Typically suitable heterocyclics include





The term "halo" as used herein means fluoro, chloro, bromo or iodo, preferably fluorine or chloro.

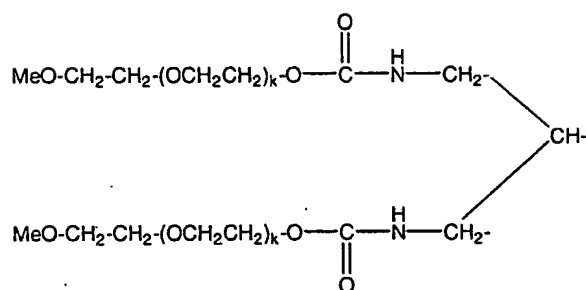
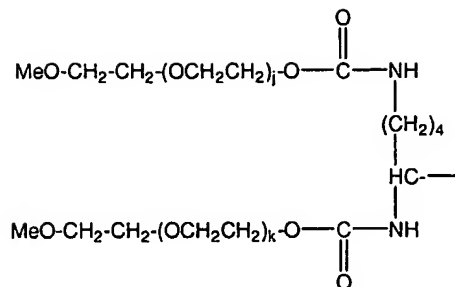
The term "straight or branched chain polyalkylene oxide polymer conjugate" as used herein means a (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide polymer having a terminal spacer group(SG). Typically suitable (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide polymers having a terminal spacer group(SG) include .



$m = 0$  to 100;  $n = 0$  to 6000;  $t = 1$  to 4; and  $q = 1$  to 5000; and SG is as defined hereinbelow.

The (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide conjugates include (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyethylene oxide polymer conjugates, especially methoxy-CH<sub>2</sub>-CH<sub>2</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>j</sub>-SG .and (C<sub>1</sub>-C<sub>3</sub>)alkoxy polypropylene oxide polymer conjugates, especially -(C<sub>1</sub>-C<sub>3</sub>)alkoxy C(CH<sub>3</sub>)H-CH<sub>2</sub>-(OC(CH<sub>3</sub>)HCH<sub>2</sub>)<sub>j</sub>-SG. Typically suitable branched-chain polyethylene oxide polymer conjugates include the following

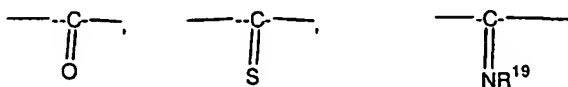




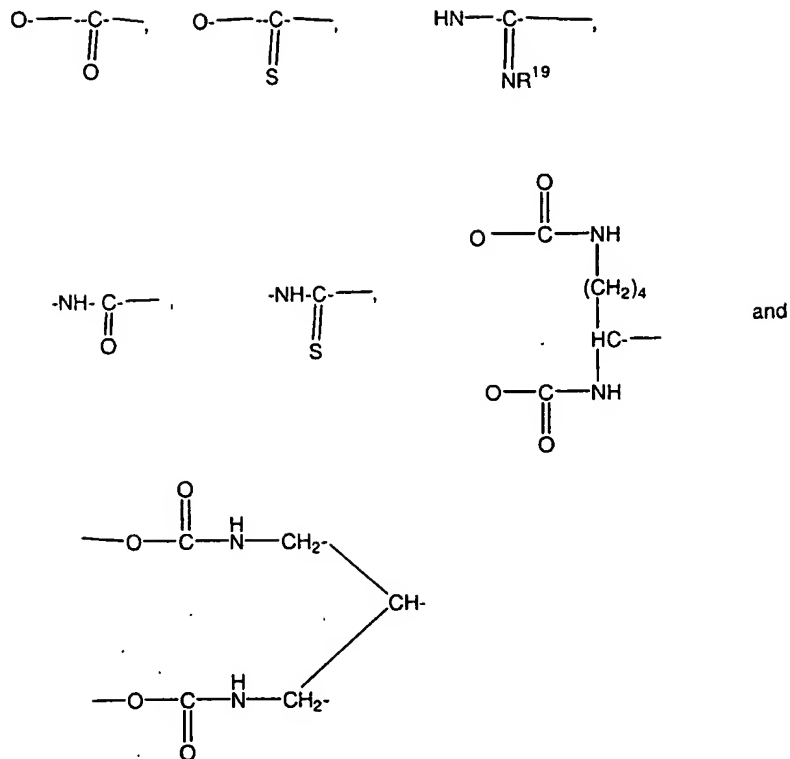
wherein j and k are independently 400 to 600, preferably each is 420 to 460.

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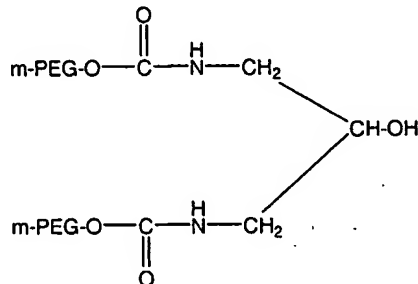
Typically suitable spacer groups (SG) include







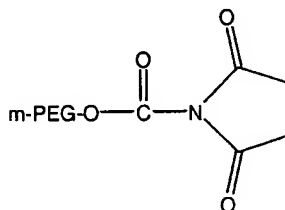
These branched chain polymer conjugates are disclosed in EP0 809 996 and are available from Shearwater Polymers Inc., Huntsville, Ala. Other branched chain polyalkylene oxide conjugates are the methoxy polyethylene glycol conjugates disclosed in U.S. Patent No.5,642,575. See especially the examples on col 9, line 38 to col.13, line 60. Methoxy polyethylene glycols (m-PEG-) are available from Union Carbide Corp., Danbury, Conn. Exemplary methoxy polyethylene glycol conjugates are disclosed in U.S. Patent No.5,642,575. Include





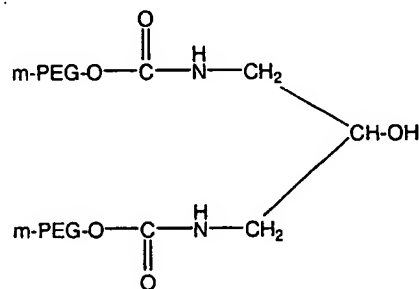
These branched chain polymer conjugates may be prepared in accordance with the procedures of U.S. Patent No 5,122,614: using for example methoxy-polyethylene glycol ("m-PEG") having a MW = 5000 to form methoxy-poly(ethylene glycol)- N--succinimidyl carbonate(SC-PEG);

5



In accordance with the procedures of U.S. Patent No.5,642,575., SC-PEG is reacted with 1,3-diamino-2-propanol in an aprotic solvent such as methylene chloride at room temperature to give the compound of the formula A

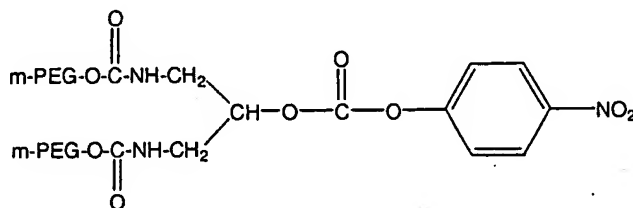
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A

The compound of the formula A is treated with an activating group, e.g., p-nitrophenyl chloroformate under anhydrous conditions in the presence of a base such as pyridine to give the activated compound of formula B:

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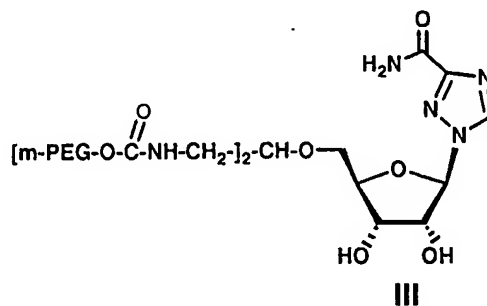


B

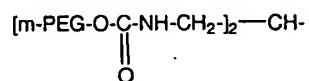
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Reaction of the activated compound of formula B: with benzylidene ribavirin-  
compound 2 of Example 1 of this invention- provides the the branched chain  
methoxy-polyethylene glycol conjugate of ribavirin of formula III;



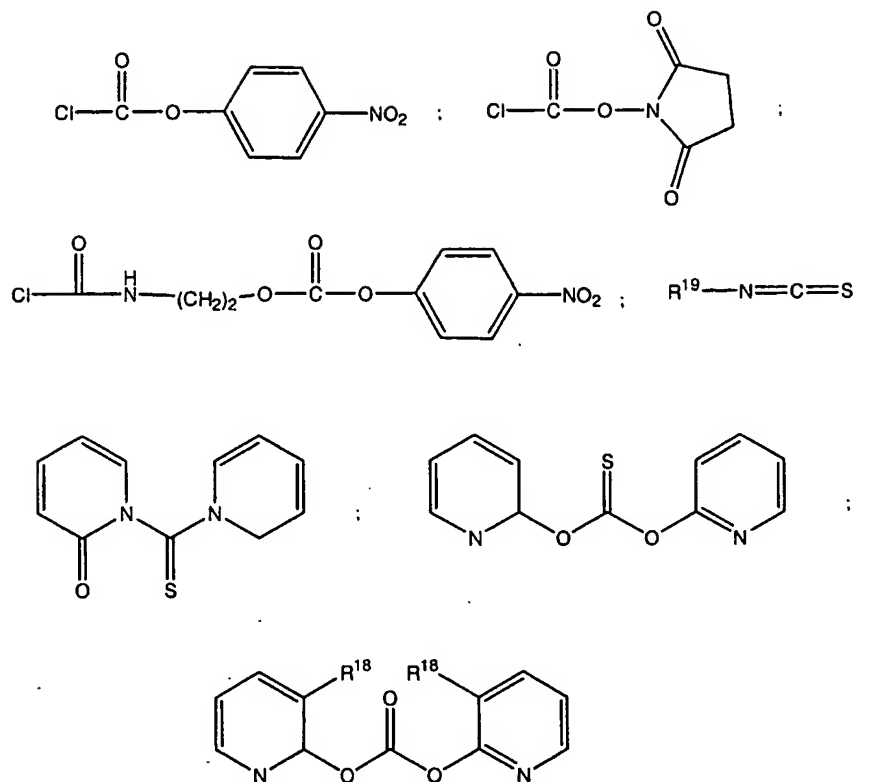
5 wherein R<sup>50</sup> is



and wherein m-PEG is methoxy-polyethylene glycol.

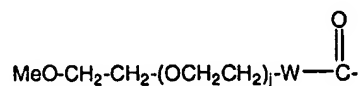
10 Typically suitable activating groups include





wherein  $\text{R}^{19}$  is  $(\text{C}_1-\text{C}_8)$ alkyl or  $(\text{C}_3-\text{C}_8)$ cycloalkyl, and preferably  $\text{R}^{19}$  is methyl;  $\text{R}^{18}$  is H, alkanoyl or alkyl and preferably  $\text{R}^{18}$  is methyl. See European Patent applications  
 5 EP 0510356 and EP0236987 for the preparation of the above listed activating groups.

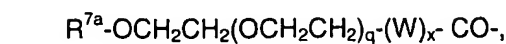
Preferred straight chain polyalkylene oxide polymer conjugates include  $(\text{C}_1-\text{C}_3)$ alkoxy-polyalkylene oxide polymer especially methoxy-polyethylene glycol  
 10 conjugates such as wherein j is 400 to 800



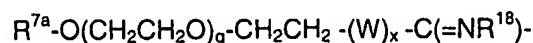
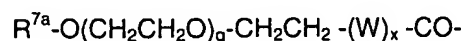
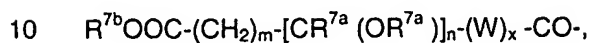
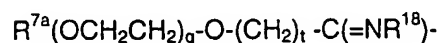
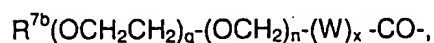
15 In preferred embodiments of the present invention, the compounds of formula I have at least one of  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^5$  equal to a straight chain polyalkylene oxide polymer



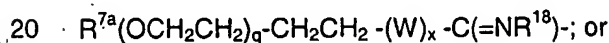
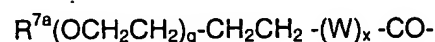
conjugate ; wherein the straight chain polyalkylene oxide polymer conjugate is selected from



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W = -O- or -NR<sup>18</sup>-; and R<sup>18</sup> = H;

m = 0 to 100; n = 0 to 6000; t = 1 to 4; and q = 1 to 5000.

25

In another preferred embodiment of the present invention, the compounds of formula I have R<sup>2</sup> = R<sup>3</sup> = H and R<sup>5</sup> is one of the above listed straight chain polyalkylene oxide polymer conjugates.

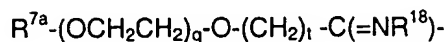
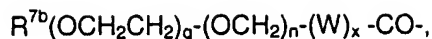
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In another preferred embodiments of the present invention, the compounds of formula II have at least one of R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> equal to a straight chain polyalkylene oxide polymer conjugate; wherein the straight chain polyalkylene oxide polymer conjugate is selected from

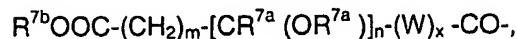
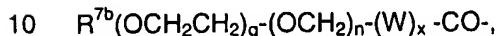
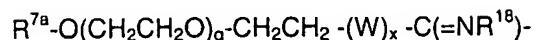
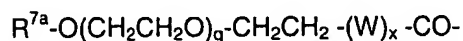
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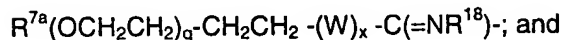
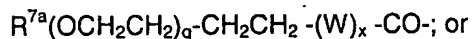




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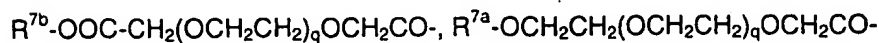
and

$m = 0 \text{ to } 100; n = 0 \text{ to } 6000; q = 1 \text{ to } 5000; t = 1 \text{ to } 4; \text{ and } x = 0 \text{ or } 1.$

25 In another preferred embodiment of the present invention, the compounds of formula II have  $R^2 = R^3 = H$  and  $R^5$  is one of the above listed straight chain polyalkylene oxide polymer conjugates.

30 In more preferred embodiments of the present invention, (a) wherein the compounds of formula I have  $R^2 = R^3 = H$  and (b) wherein the compounds of formula II have  $R^2 = R^3 = H$ ,  $R^5$  and  $R^5$  are independently one of the following preferred straight chain polyalkylene oxide polymer conjugates:

35

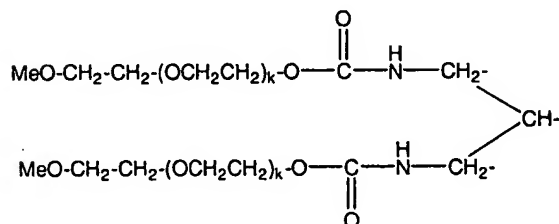
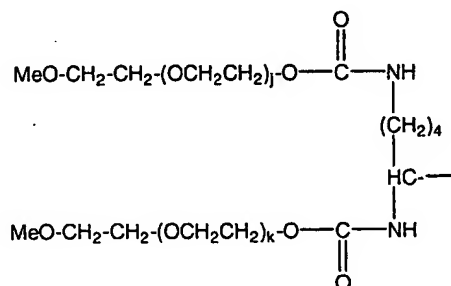




- $R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-CO-$ ,  $R^{7a}-OCH_2CH_2(OCH_2CH_2)_q-NH-CO-$  ;  
 $R^{7a}-OCH_2CH_2(OCH_2CH_2)_q-O-CO-$ ;  $R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-NH-CO-$ ;  
 $R^{7a}-O(CH_2CH_2)_q-CH_2CH_2-NH-C(=NR^{18})-$ ;  
 $R^{7a}(OCH_2CH_2)_q-CH_2CH_2-NH-C(=NH)-$  ; or  
 $R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-CO-$ ; and

$n = 0$  to  $6000$ ; and  $q = 1$  to  $5000$ .

Exemplary methoxy-polyethylene glycol conjugates include







The methoxy- polyethylene glycol conjugates can readily be prepared and their molecular weight determined by one skilled in the art view of known methods such as described in European Patent Applications EP0236987 and EP0510356. The starting polyethylene glycols (PEG) and PEG monomethyl ethers of various molecular weights e.g. 750, 1900, 5000, 10,000 can readily be prepared by methods known in the art or can be obtained from commercial sources.

In a preferred embodiment of the present invention, compounds of formula I have  $R^2=R^3=H$  and  $R^5$  equal to  $R^6(W)_x\text{CO-}$ ,  $(\text{HO})_2\text{P=O-}$  or  $R^6(W)_x\text{PO(OH)-}$ . In the preferred embodiments of  $R^6\text{-(W)}_x\text{CO-}$  and  $R^6(W)_x\text{-PO(OH)-}$ ,  $W=\text{O}$  or  $\text{NH}$  and  $x=0$  or  $1$ . In other preferred embodiments of  $R^6\text{-(W)}_x\text{CO-}$  and  $R^6(W)_x\text{P(OH)O-}$  include  $R^{17}(\text{CH}_2)_m\text{-NR}^{7b}\text{R}^{7a}\text{-(CH}_2)_n\text{OCO-}$  and  $R^{17}(\text{CH}_2)_m\text{-NR}^{7b}\text{R}^{7a}\text{-(CH}_2)_n\text{-O-PO(OH)}$ , wherein  $m=0$  to  $4$  and  $n=0$  to  $4$ ; and  $R^{17}$  is  $\text{H}$ ,  $\text{Me}$ ,  $\text{MeCO-}$  or  $\text{Me}_2\text{N-}$ , and  $R^{7a}\text{R}^{7b}\text{N(CH}_2\text{)}_f\text{-(CHR}^{7a}\text{)}_e\text{OCO-}$  or  $R^{7a}\text{R}^{7b}\text{N(CH}_2\text{)}_f\text{-(CHR}^{7a}\text{)}_e\text{CO-}$ ; wherein  $f=0$  to  $4$  and  $e=1$  to  $5$ , and  $R^{7a}\text{R}^{7b}\text{N}$  is  $\text{Me}_2\text{N-}$ ,  $\text{MeHN-}$  or  $\text{MeCONH-}$ .

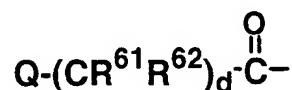


In most preferred embodiments of the compounds of formula I,  $x$  in  $R^6(W)_xCO-$ , is equal to 0.

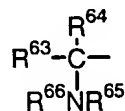
5 In another preferred embodiment of the compounds of formula I, one of  $R^2$ ,  $R^3$  or  $R^5$  is  $R^6CO$  and  $R^6CO$  is a natural or unnatural  $\alpha$ -amino acid residue.

In another preferred embodiment of the compounds of formula II, one of  $R^z$ ,  $R^3$  or  $R^5$  is a natural or unnatural  $\alpha$ -amino acid residue.

10 The term "a natural or unnatural  $\alpha$ -amino acid residue" as used herein means a residue represented by the formula



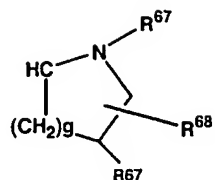
15 wherein  $Q$  is



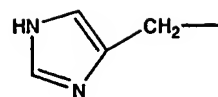
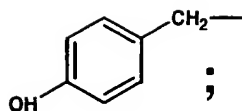
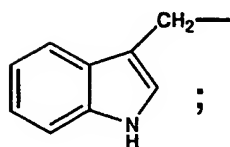
wherein  $R^{61}$  and  $R^{62}$  are independently H, alkyl, alkenyl, alkynyl,  $(C_3-C_7)$ cycloalkyl, arylalkyl, or alkyl, alkenyl, alkynyl,   
 20  $(C_3-C_7)$ cycloalkyl, arylalkyl, substituted by halo, OH, SH,  $CF_3$ ,  $SR^{67}$ ,  $OR^{67}$  or  $NR^{65}R^{68}$  or wherein  $R^{61}$  and  $R^{62}$  taken together with the carbon atom in  $(CR^{61}R^{62})$  form a cyclopropane, cyclobutane, cyclopentane, or cyclohexane.;

wherein  $R^{63}$  and  $R^{64}$  are independently H, alkanoyl, alkyl, aryl, arylalkyl, alkenyl, alkynyl,   
 25 or alkanoyl, alkyl, aryl, arylalkyl, alkenyl, alkynyl substituted by halo, OH, SH,  $CF_3$ ,  $SR^{67}$ ,  $OR^{67}$ ; or  $R^{63}$  and  $R^{64}$  are independently





or



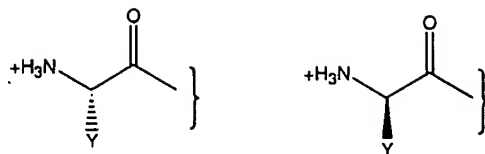
wherein  $R^{67}$  is H, alkyl, alkanoyl, alkenoyl, aryl, arylalkyl, alkenyl, alkynyl, or, alkyl, aryl, arylalkyl, alkenyl, alkynyl substituted by halo, OH, SH,  $CF_3$ , alkanoylthienyl, or alkanoyloxy;

wherein  $R^{68}$  is H, alkyl, aryl, arylalkyl, alkenyl, or alkynyl;

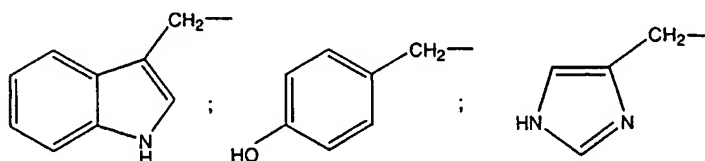
and g is 0, 1 or 2; d is 1 or 2;

In a more preferred embodiments of the compounds of formulas I and II, the preferred natural or unnatural  $\alpha$ -amino acid residues are selected from-



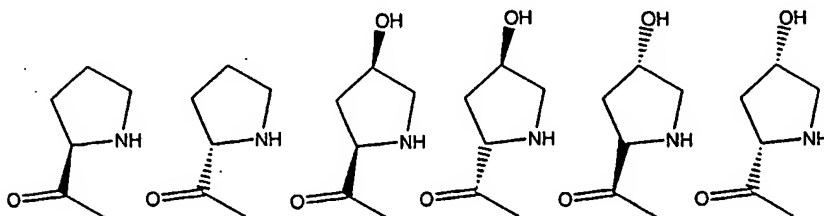


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



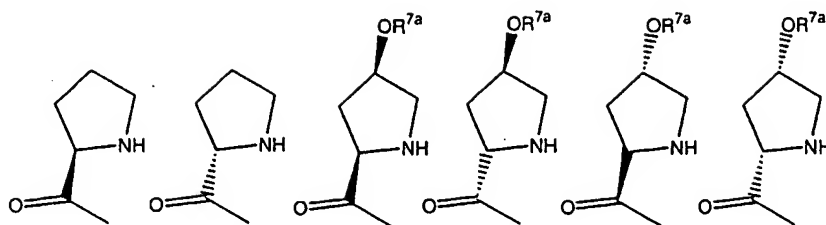
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof;

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.



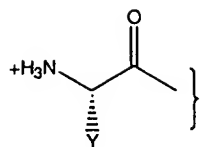


wherein R<sup>7a</sup> is as defined hereinabove; or a pharmaceutically acceptable salt thereof.

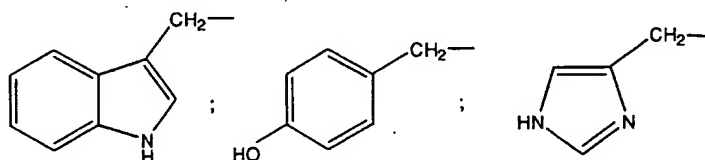
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In another more preferred embodiment of the compounds of formulas I and II, the preferred natural  $\alpha$ -amino acid residues are selected from



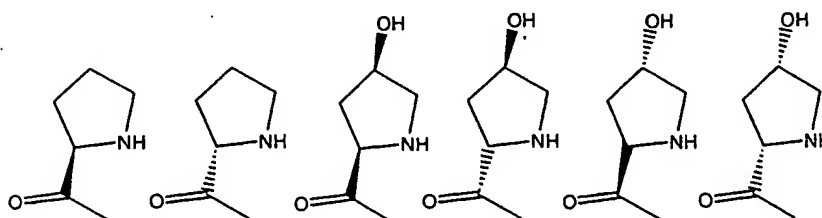


Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



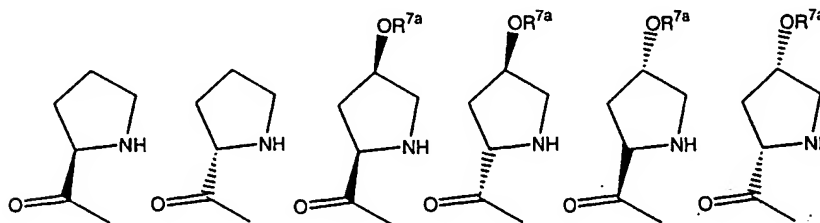
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof

or Y taken together with the  $\alpha$  carbon and N form



or

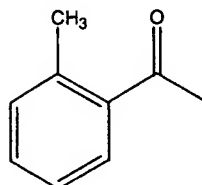
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wherein R<sup>7a</sup> is as defined hereinabove;  
or a pharmaceutically acceptable salt thereof.



Other preferred embodiments for  $R^6CO$  in the compounds of formula I include



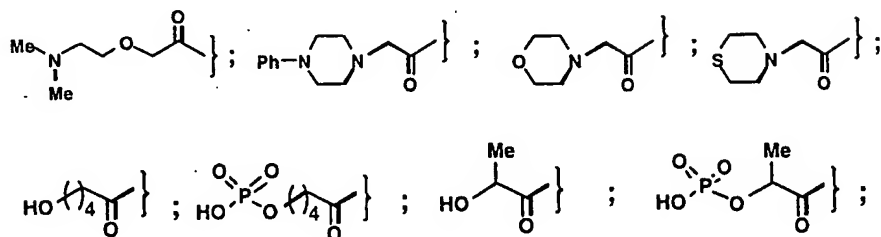
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$(CH_3)_3CO-$ ,  $C_6H_5CO-$ ,  $(HO)_2PO-$  - and

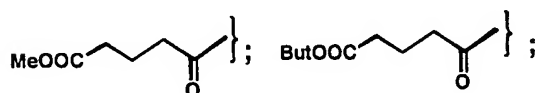
$L-C_6H_5CH_2OCONHCH(CH_3)CO-$ , i.e.,  $C_6H_5CH_2OCONHCH$

10

or  $R^6CO$  is



\*(and substituted Ph)



15

or a pharmaceutically acceptable salt thereof;

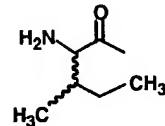
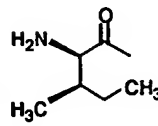
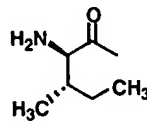
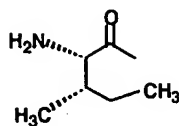
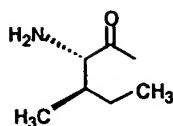
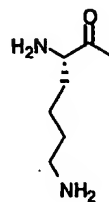
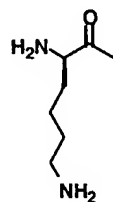
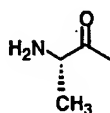
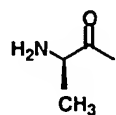
wherein Ph is phenyl and phenyl substituted by halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy.



The most preferred natural or unnatural amino acid residues in the compounds of formulas I and II are represented by the formulas in Table AA herein below:

**TABLE AA**

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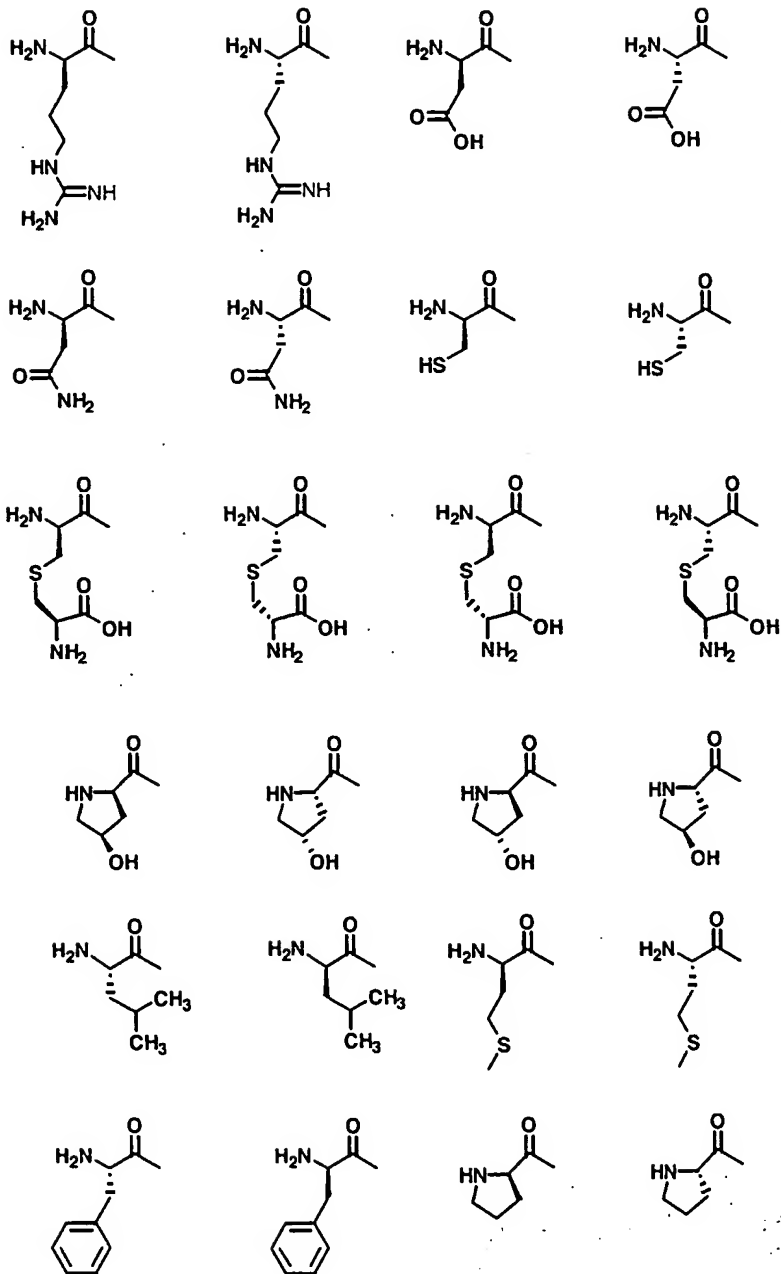
TABLE AA cont.



TABLE AA cont.

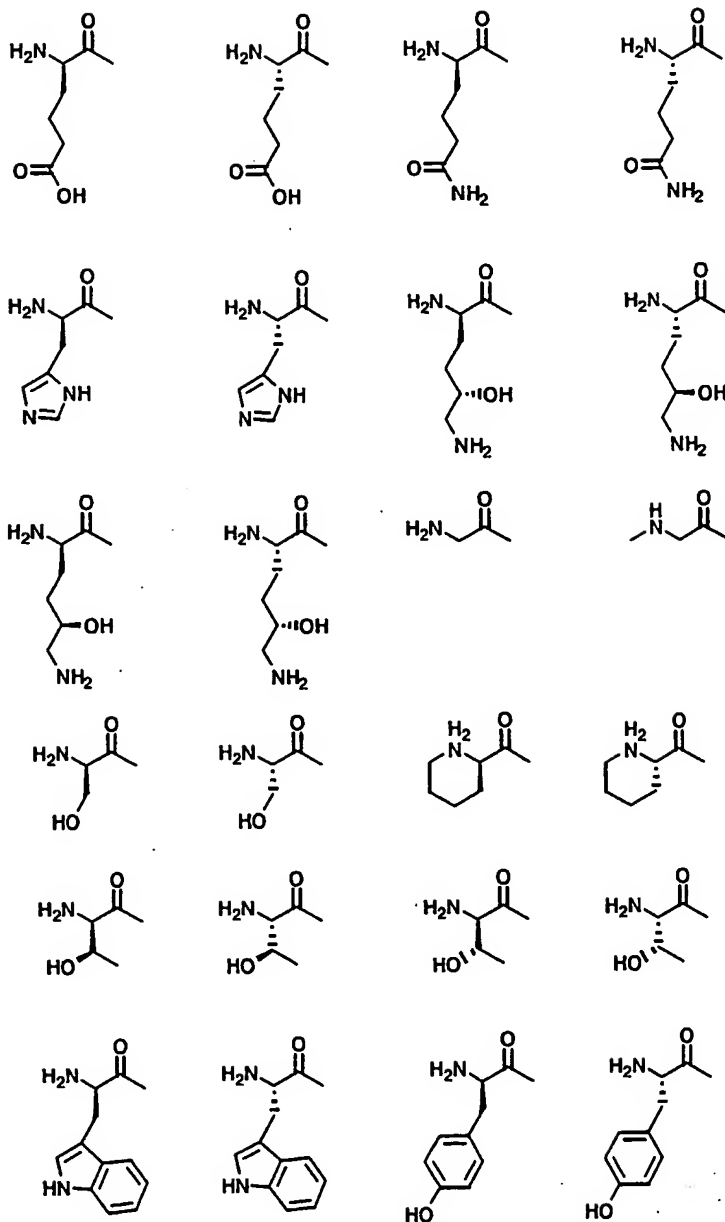
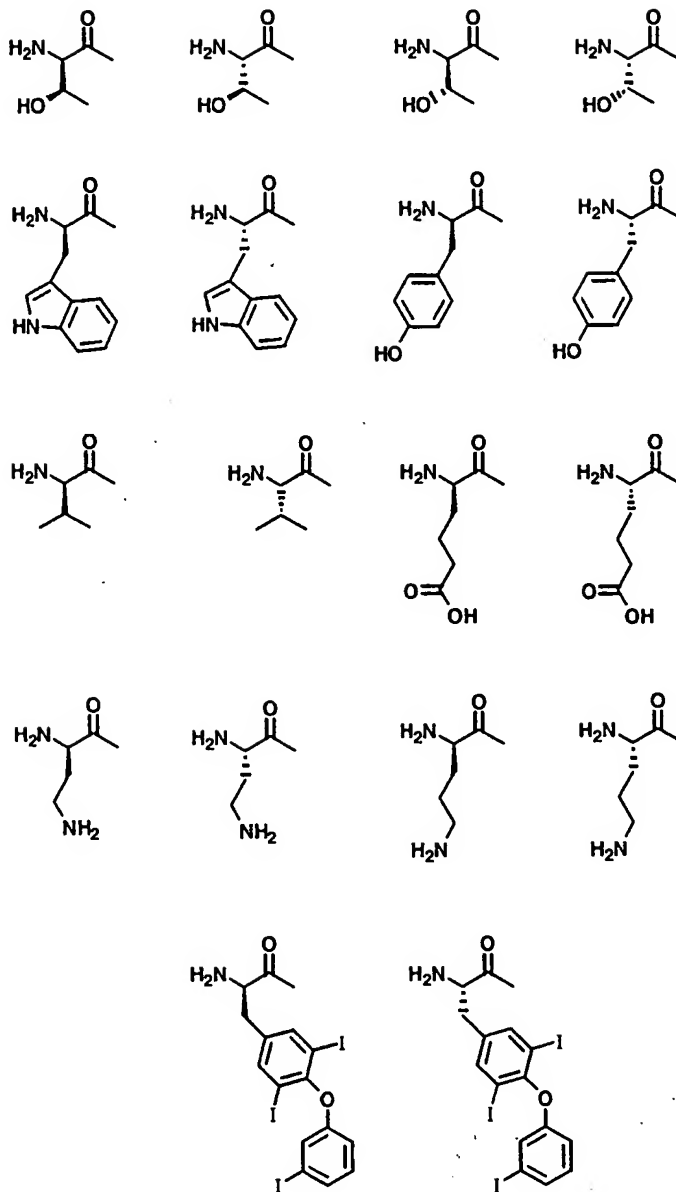




TABLE AA cont.



The compounds of formulas I to IV metabolize *in vivo* into ribavirin and are useful for treating susceptible viral infections treatable with ribavirin, alone, or in combination with other ant-viral therapies .eg., interferon-alfa, and so- called Highly Active Antiretroviral Therapy ("HAART"). A-M. Vandamme et al., Antiviral Chemistry &

5 Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART") ; HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse trans-cryptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). The treating of patients having chronic  
10 hepatitis C with the compounds of formulas I-VIII is performed as part of a combination therapy with interferon-alfa, including interferon alfa-2a, interferon alfa-2b, consensus interferon especially interferon alfa-2b as well as pegylatyed interferon alfa-2a and pegylatyed interferon alfa-2b.

15 The present invention provides methods and pharmaceutical compositions containing a compound of formulas I-IV for treating susceptible viral infections , especially hepatitis C viral infections.

The term "susceptible viral infections" as used herein means viral infections  
20 caused by a wide range of RNA and DNA viruses, including, but not limited to, the families of viruses such as flaviruses-including the genus flavirus, pestivirus of which Kunjin virus is a member, and hepavirus of which hepatitis C virus is a member, and arbovirus of which the West Nile virus is a member- orthomyxoviruses, paramyxoviruses, arenaviruses, bunyaviruses, herpes viruses, adenoviruses,  
25 poxviruses, and retroviruses.

Typical suitable "susceptible viral infections" include influenza A and B viral infections; parainfluenza viral infections, respiratory syncytial virus("RSV") infections such as RSV bronchiolitis and RSV pneumonia especially such RSV infections in  
30 children and infants as well as RSV pneumonia in patients with preexisting cardiopulmonary disease, measles viral infections, Lassa fever viral infections, Korean Haemorrhagic fever infections, hepatitis B viral (HBV) infections, Crimean-Congo Haemorrhagic and HCV infections and HIV-1 infections, encephalitis infections such as caused by West Nile virus or Kunjin virus or the St. Louis encephalitis infections as well



as viral infections found in immunocompromised patients. Other susceptible viral infections are disclosed in USP 4,211,771 at column 2, line 21 to column 3 line 37; doses and dose regimens and formulations are disclosed at column 3, line 4 to column 9, line 5; see also Canadian Patent No. 1,261, 265. Sidwell, R.W., et al. Pharmacol. Ther., 1979, Vol 6 pp 123-146 discloses that the in vivo antiviral experiments conducted with ribavirin generally confirm one broad-spectrum antiviral activity seen in vitro and states that the efficacy of ribavirin is quite dependent upon the site of infection; the manner of treatment; the age of the animal and the virus dosage utilized. Tables 4 and 5 on page 127 list the RNA and DNA virus infections significantly inhibited in vivo by ribavirin.

The *in vitro* inhibitory concentrations of ribavirin are disclosed in Goodman & Gilman's "The Pharmacological Basis of Therapeutics", Ninth Edition, (1996) McGraw Hill, NY, at pages 1214-1215. The Virazole product information discloses a dose of 20 mg/mL of Virazole aerosol for 18 hours exposure in the 1999 Physicians Desk Reference at pages 1382 - 1384.

Ribavirin dosage and dosage regimens are also disclosed by Sidwell, R.W., et al. Pharmacol. Ther 1979 Vol 6. pp123-146 in section 2.2 pp 126-130. Fernandes, H., et al., Eur. J. Epidemiol., 1986, Vol 2(1) pp1-14 at pages 4-9 disclose dosage and dosage regimens for oral, parenteral and aerosol administration of ribavirin in various preclinical and clinical studies.

The term "patients having hepatitis C infections" as used herein means any patient-including a pediatric patient- having hepatitis C and includes treatment-naïve patients having hepatitis C infections and treatment-experienced patients having hepatitis C infections as well as those pediatric, treatment-naïve and treatment-experienced patients having chronic hepatitis C infections.

These patients having hepatitis C include those who are infected with multiple HCV genotypes including type 1 as well as those infected with, e.g., HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.



The term "treatment-naive patients having hepatitis C infections" as used herein means patients with hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

5           The term "treatment-experienced patients having hepatitis C infections" as used herein means patients with hepatitis C who have been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa, including relapsers and non-responder.

10           The term "relapsers" as used herein means treatment-experienced patients with hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

15           The term "non-responders" as used herein means treatment-experienced patients with hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

20           When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), preferably in the range of about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW), or is in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.25 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, or is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, most preferably is in the range of



about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 0.75 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week.

5           When the pegylated interferon-alfa administered to pediatric patients is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice  
10 a week(BIW), more preferably about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), or about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week(BIW), more preferably about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b  
15 administered once a week, or preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered in single or divided doses, preferably once a week (QW) or twice a week(BIW), more preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b  
20 administered twice a week, and most preferably about 2.25 to about 2.6 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 1.1 to about 1.3 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week(BIW).

25           When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in accordance with the present invention, is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 150 micrograms to about 250  
30 250 micrograms twice a week, preferably about 100 micrograms to about 125 micrograms twice a week.



When the pegylated interferon-alfa administered to a pediatric patient is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in accordance with the present invention, is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 300  
5 micrograms to about 375 micrograms QW or the therapeutically effective amount of pegylated interferon alfa-2a administered to a pediatric patient is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 150 micrograms to about 190 micrograms once a week

10 The esters of ribavirin represented by formulas I-IV are administered to the patient having chronic HCV in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of esters of ribavirin represented by formulas I-IV . The  
15 amount of esters of ribavirin represented by formulas I-IV administered concurrently with the pegylated interferon-alfa is from about 200 to about 1600 mg per day, preferably about 300 to about 1200 mg/day or about 400 to about 800 mg day and most preferably about 400 to about 600 mg a day. The pegylated interferon-alfa dose is also preferably administered to the pediatric patient during the same period of time that such patient  
20 receives doses of the esters of ribavirin represented by formulas I-IV . The amount of the 5'-amino acid esters of ribavirin represented by formulas I-IV administered to the pediatric patient having chronic HCV concurrently with the interferon-alfa is from about 1 to about 30 mg per kilogram per day, preferably from about 4 to about 15 mg per kilogram per day, more preferably about 6, 8 or 15 mg per kilogram per day, most  
25 preferably about 8 to 10 mg per kilogram per day in divided doses.

Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by sub-cutaneous(SC), intravenous(IV), or intramuscular(IM) injection. The  
30 compounds represented by formulas I-IV may be administered orally in capsule, tablet, or liquid form, intranasally as an aerosol by nasal spray or parenterally, preferably by SC, IV, or IM injection. The esters of ribavirin represented by formulas I-IV may be orally



administered in association with the parenteral administration of pegylated interferon-alfa . Of course, other types of administration of both medicaments, as they become available, are contemplated, such as transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient

The term "interferon-alfa" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b, such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a, such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alfa-2c, such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons, such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon, such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

25

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG<sub>12000</sub>-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alfa" and "PEG<sub>12000</sub>-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane

30



linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG<sub>12000</sub>-interferon alfa-2b is prepared by attaching a PEG polymer  
5 to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG<sub>12000</sub> molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG<sub>12000</sub> attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery  
10 of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

Other pegylated interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include  
15 other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer  
20 conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

25 Pharmaceutical composition of pegylated interferon alfa suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients, e.g., sucrose, carriers, e.g., human or  
recombinant plasma albumin, tonicity agents, e.g. NaCl, preservatives, e.g., thimerosal,  
30 cresol or benyl alcohol, and surfactants, e.g., tweens or polysorbates in sterile water for injection. The pegylated interferon alfa may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored



between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled  
5 vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

10

A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

15

(a) elevated ALT,

(b) positive test for anti-HCV antibodies,

(c) presence of HCV as demonstrated by a positive test for the presence of HCV-RNA in the serum,

20

(d) clinical stigmata of chronic liver disease,

(e) hepatocellular damage.

25

The combination therapy of pegylated interferon-alfa and the esters of ribavirin represented by formulas I-IV may also be administered in association with anti-retroviral therapy, e.g., HAART, to the patient co-infected with the HIV-1 and HCV infection and exhibiting one or more of the above signs or symptoms in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms of the HCV infection, and to  
30 lower the HIV-1-RNA and HCV-RNA serum levels each by at least a power of ten, and preferably to eradicate detectable HCV-RNA at least by the end of about 20 to about 50 weeks, preferably at least 24 weeks to 48 weeks and to maintain no detectable HCV-



RNA for at least 24 weeks after the end of the about 20 to about 50 weeks.

Administration of the compounds represented by formulas I - IV may be discontinued after the end of the second time period depending upon the judgment of the attending clinician.

5

The term "no detectable HCV-RNA" in the context of the present invention means that there are fewer than 100 copies of HCV-RNA per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is 100 copies/mL. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

15

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

25

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

30



Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted,  
5 shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as  
10 are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired  
15 purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular compound and particular  
20 application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as  
25 required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended  
30 daily dosage regimen for oral administration can range from about 1 mg/kg/day to about 100 mg/kg/day, in two to four divided doses.



In a preferred embodiment of the present invention, those patients co-infected with HIV-1 and HCV infections are treated with pegylated interferon alfa in combination with the preferred 5'-amino acid esters of ribavirin represented by formulas III to VIII and a HAART combination considered appropriate by the attending clinician and the patient..

5 See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 1998, 339:1493-1499).

The preferred compounds of formulas I-IV are useful for treating patients having susceptible viral infections, e.g., chronic hepatitis C. The compounds of formulas III-VIII metabolize *in vivo* into ribavirin and are useful for treating susceptible viral infections treatable with ribavirin, alone, or in combination with other anti-viral therapies, e.g., interferon-alfa and HAART. The treating of patients having chronic hepatitis C with the compounds of formulas I-IV is performed as part of a combination therapy with interferon-alfa, especially interferon alfa-2b.

15

Compounds of formulas I-IV metabolize *in vivo* into ribavirin and produce higher plasma concentrations of ribavirin after oral administration of a compound of formulas I-IV to animals compared to administration of ribavirin.

20

The pharmaceutical compositions of the esters of ribavirin of the present invention (represented by formulas III & IV) may be adapted for any mode of administration e.g., for oral, parenteral, e.g., subcutaneous ("SC"), intramuscular ("IM"), intravenous ("IV") and intraperitoneal ("IP"), topical or vaginal administration or by inhalation (orally or intranasally). Preferably the ribavirin compounds represented by formula I are administered orally.

25

Such compositions may be formulated by combining a compound of formulas I-IV or an equivalent amount of a pharmaceutically acceptable salt of compound I with an suitable, inert, pharmaceutically acceptable carrier or diluent which may be either solid or liquid. The compounds of formulas I-IV are preferably converted into the pharmaceutically acceptable acid addition salts by adding to compounds of formulas I-

30



IV an equivalent amount (or two equivalents in the case of for example the lysine ester) of a pharmaceutically acceptable acid. Typically suitable pharmaceutically acceptable acids include the mineral acids, e.g.,  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$ ,  $\text{HCl}$ ,  $\text{HBr}$ , organic acids, including, but not limited to, acetic, trifluoroacetic, propionic, lactic, maleic, succinic, tartaric, glucuronic and citric acids as well as alkyl or arylsulfonic acids, such as p-toluenesulfonic acid, 2-naphthalenesulfonic acid, or methanesulfonic acid.

Typically suitable pharmaceutically acceptable salts include the following anions: acetate, adipate, besylate (benzenesulfonate), bromide, camsylate[(+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate], chloride, citrate, edisylate(1,2-ethanedisulfonate), estolate(dodecyl sulfate), fumarate, gluceptate(glucoheptonate), gluconate, glucuronate, hippurate, hyclate(hydrochloride, hemiethanolate), hydrobromide, hydrochloride, iodide, isethionate (2-hydroxyethanesulfonate), lactate, lactobionate, maleate, mesylate (methanesulfonate), methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate [4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate]], phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate(p-toluenesulfonate), triethiodide.;

and the following cations: benzathine (N,N-bis(phenylmethyl)-1,2-ethanediamine), calcium, diolamine (2,2-iminobis(ethanol)), meglumine[1-deoxy-1-(methylamino)-D-glucitol], olamine(2-aminoethanol), potassium, procaine, sodium tromethamine [2-amino-2-(hydroxymethyl)-1,3 propanediol,] and zinc.

The preferred pharmaceutically acceptable salts are trifluoroacetate, tosylate, mesylate, and chloride.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for



various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an  
5 example may be mentioned water or water-propylene glycol solutions for parenteral  
injection. Solid form preparations may be converted into liquid preparations shortly  
before use for either oral or administration. Parenteral forms to be injected  
intravenously, intramuscularly or subcutaneously are usually in the form of sterile  
solutions and may contain tonicity agents (salts or glucose), and buffers. Opacifiers may  
10 be included in oral solutions, suspensions and emulsions. Liquid form preparations may  
also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in  
powder form, which may be in combination with a pharmaceutically acceptable carrier,  
15 such as an inert compressed gas, e.g., nitrogen.

Also included are solid form preparations that are intended to be converted,  
shortly before use, to liquid form preparations for either oral or parenteral administration.  
Such liquid forms include solutions, suspensions and emulsions.

20

The compounds of the invention may also be deliverable transdermally. The  
transdermal compositions can take the form of creams, lotions, aerosols and/or  
emulsions and can be included in a transdermal patch of the matrix or reservoir type as  
are conventional in the art for this purpose.

25

Preferably, the pharmaceutical preparation is in a unit dosage form. In such  
form, the preparation is subdivided into suitably sized unit doses containing appropriate  
quantities of the active component, e.g., an effective amount to achieve the desired  
purpose.

30

The effective amount or therapeutically effective amount of compound of the  
present invention in a unit dose of preparation may be varied or adjusted from about 1



mg to about 1600 mg per day, preferably from about 1mg to about 1200 mg per day, or about 300 mg to about 1200 mg per day, more preferably from about 1 mg to about 800 mg per day, or about 400 mg to about 800 mg per day and most preferably from about 1 mg to about 100 mg per day from about 400 mg to about 600 mg per day, in single or  
5 divided doses, according to the particular compound and particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience,  
10 the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the  
15 judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. The dose of the preferred compounds of formulas I - IV should be chosen to provide steady state plasma concentrations of ribavirin in the range of about 0.1ug/mL to about 100 ug/mL, preferably in the range of about 0.1ug/mL to about 50 ug/mL, more preferably in the range of  
20 about 1 ug/mL to about 3 ug/mL, and most preferably in the range of about 1.8 ug/mL to about 2.6 ug/mL. Plasma ribavirin concentrations may be determined using high pressure liquid chromatographic material with tandem mass spectrometric detection. The method was validated with respect to linearity, selectivity, precision, accuracy and has a limit of quantitation of 50 microg/mL. A typical recommended daily dosage  
25 regimen for oral administration can range from about 1 mg/kg/day to about 100 mg/kg/day, in two to four divided doses.



Ribavirin, 1- $\beta$ -D-ribofuranosyl-1H-1, 2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

5

The ribavirin derivatives of formulas I -VIII may be prepared by use of the sequences of steps illustrated in the following Schemes, and in the Examples using the compounds listed hereinafter the Schemes.

- 10 In Scheme I, compounds of formula I wherein  $R^5=R^{5a}CO-$ ,  $R^3=R^{3a}CO$  and  $R^2=H$  and  $R^5=R^{5a}CO-$  and  $R^2=R^{2a}CO-$  and  $R^3=H$  and  $R^5=R^{5a}CO-$  and  $R^3=R^2=H$ , are prepared. Compound 110 (ribavirin) and benzaldehyde are treated with  $ZnCl_2$  in excess benzaldehyde as solvent at ambient temperature (20 to 25°C) for 24 hrs. to give compound 111. Treatment of 111 with the alkanoyl chloride  $R^{5a}COCl$  in the presence of
- 15 base e.g. triethylamine ("TEA"); or with the carboxylic acid ( $R^{5a}COOH$ ) and triethylamine and coupling reagent such as dicyclohexylcarbodiimide ("DCC") produces compound 112. Removal of the acetal protecting group with trifluoroacetic acid:water (9:1,v/v) at ambient temperature for 0.25-
- 20 2 hrs, preferably about 0.05 hrs. provides compound 113. Compound 113 is converted into a mixture of compounds 114 and 115 by treatment of 113 with  $R^{3a}COOH$ , base and DCC or  $R^{3a}COCl$  and base, e.g., TEA.

Compounds 114 and 115 may be separated by standard chromatographic techniques to provide pure compounds 114 and 115.

- 25 In Scheme II, compounds of formula 1 wherein  $R^5=R^3=H$  and  $R^2-R^{2a}CO-$  are prepared from compound 110 (ribavirin). Compound 110 is treated with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane, i.e.,  $[(i-Pr)_2SiCl]_2O$ , in DMF as solvent in the presence of imidazole for 1-4 hrs. at ambient temperature to give compound 116. Treatment of 116 with  $R^{2a}COCl$  and base e.g., TEA or  $R^{2a}COOH$ , base and a coupling reagent e.g., DCC for 12-48 hrs. at ambient
- 30 temperature provides 117. Treatment of 17 with  $Bu_4NF$  in tetrahydrofuran ("THF") at ambient temperature for 1-10 hrs. provides compound 118.

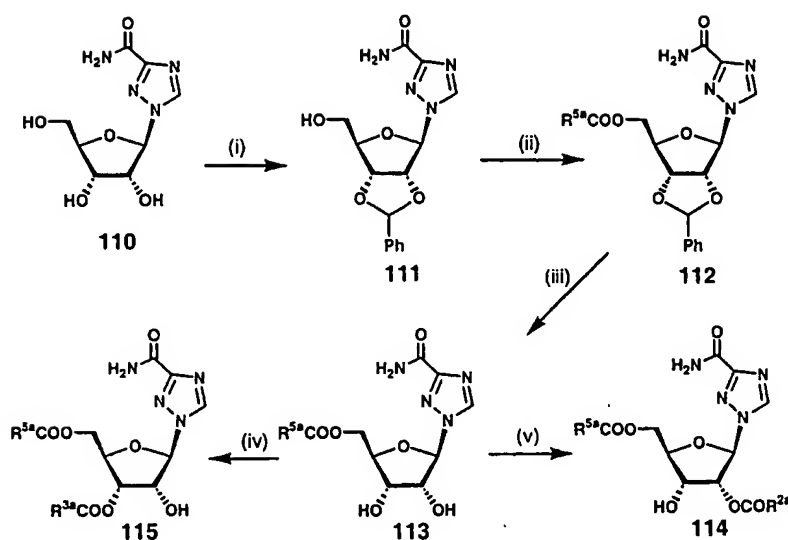


Scheme III illustrates the preparation of the compounds of formula I wherein  $R^5=R^2=H$  and  $R^3=R^{3a}CO-$  and  $R^5=R^3=H$  and  $R^2=R^{2a}CO-$  Ribavirin is treated with trityl chloride or  $[MeOC_6H_4(C_6H_5)_2]CCOCl$  and base, e.g., pyridine in a solvent DMF at ambient temperature for 6-24 hrs. to provide 119. Treatment of 119 with  $R^{2a}COCl$  and  
5 base or  $R^{2a}COOH$ , base and a coupling reagent, e.g., DCC, provides a mixture of compounds 120 and 121. The mixture is separated into the pure compounds by standard chromatographic techniques. Treatment of 120 or 121 with para-toluenesulfonic acid ("p-TsOH") in methanol in the presence of hydrogen and a palladium on charcoal catalyst at ambient temperature for 2-48 hrs. removes the  
10 protecting group to give 122 and 123, respectively. p-TsOH salt thereof.

Scheme IV illustrates preparation of the compounds of formula I wherein  $R^5=R^{5a}CO-$  or  $R^5=R^{5a}$  and  $R^3=R^2=H$ . Treatment of ribavirin 110 with  $R^{5a}COON=C(CH_3)_2$  in the presence of an enzyme, such as Novo SP 435 lipase at 65°C in a solvent such as  
15 THF or dioxane for 12-48 hrs selectively adds  $R^{5a}CO$  to the form compound 124. See also Examples 9 to 14.



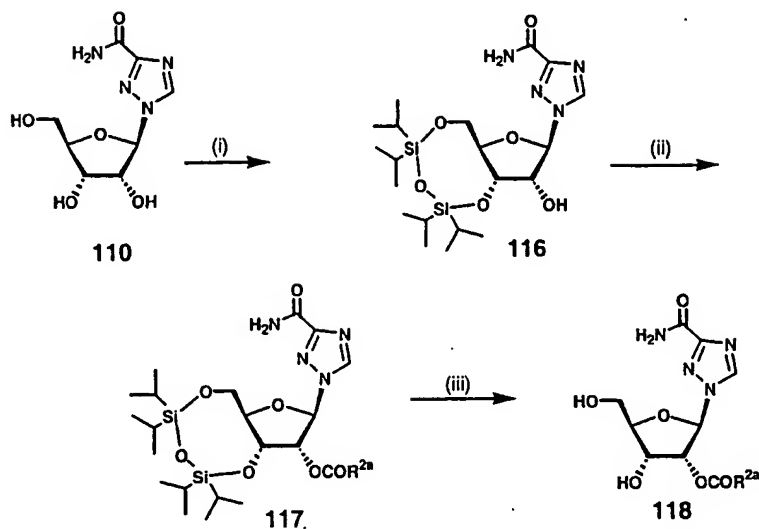
Scheme I (5'-Substitutions)



Reagents: (i)  $\text{ZnCl}_2$ ,  $\text{PhCHO}$ , (ii)  $\text{R}^{5a}\text{COCl}$ ,  $\text{Et}_3\text{N}$ ; or  $\text{R}^{5a}\text{COOH}$ ,  $\text{Et}_3\text{N}$ , coupling reagent, (iii)  $\text{TFA-H}_2\text{O}$  (9:1), (iv)  $\text{R}^{3a}\text{COOH}$  or  $\text{R}^{3a}(\text{W})\text{xCOOH}$ , coupling reagent, base; or  $\text{R}^{3a}\text{COCl}$ , or  $\text{R}^{3a}(\text{W})\text{xCOCl}$ , base, (v)  $\text{R}^{3a}\text{COOH}$ , coupling reagent, base; or  $\text{R}^{3a}\text{COCl}$ , base



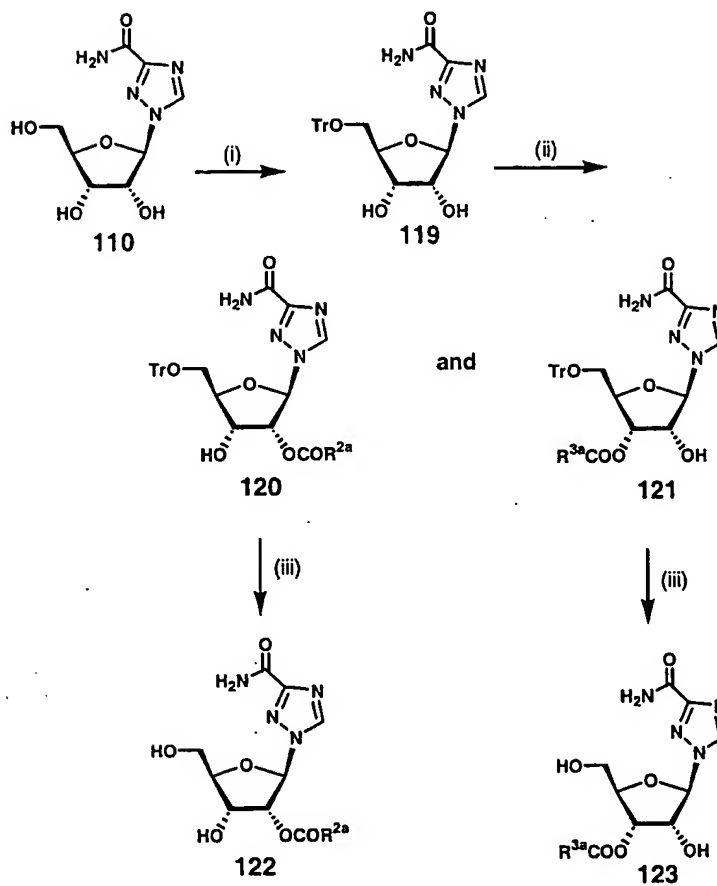
Scheme II (2'-Substitutions)



**Reagents:** (i)  $(i\text{-Pr})_2\text{SiCl}_2\text{O}$ , imidazole, DMF; (ii)  $\text{R}^{2a}\text{COCl}$ , base; or  $\text{R}^{2a}\text{COOH}$ , coupling reagent, base; (iii)  $\text{Bu}_4\text{NF}$ , THF



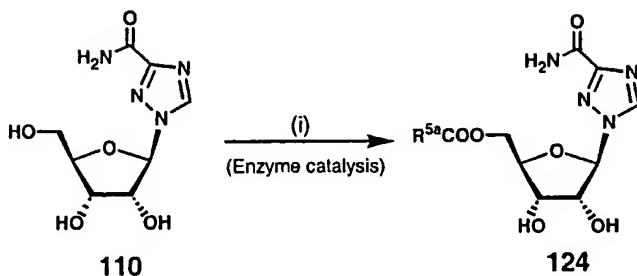
Scheme III (2' and 3'-Substitutions)



Reagents: (i) TrCl, base; (ii) R<sup>2a</sup>COCl, base; or R<sup>2a</sup>COOH, base, coupling reagent; (iii) TsOH, MeOH, H<sub>2</sub>, Pd/C

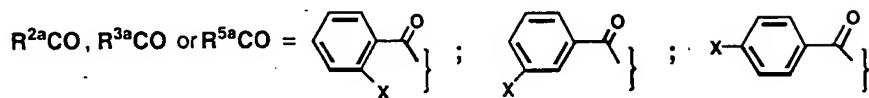


### Scheme IV (5'-Substitutions)

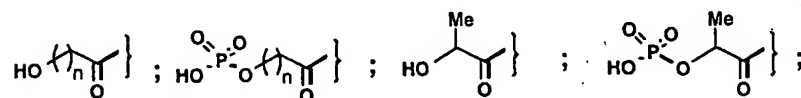
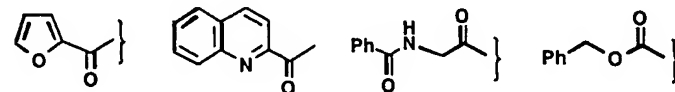
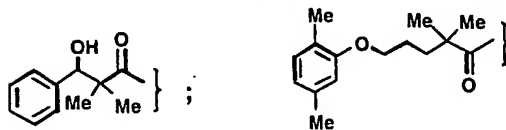
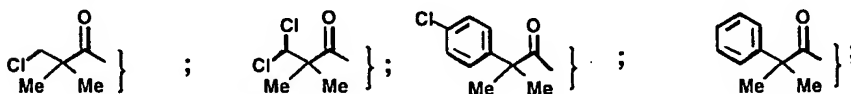
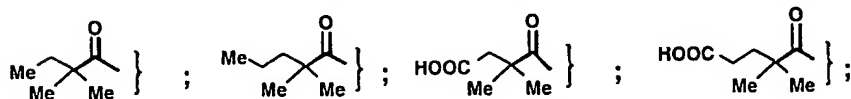


**Reagents:** (i)  $R^{5a}-C(=O)-O-N=C(CH_3)_2$ , SP435 lipase, 65°C, THF

**Examples for all schemes:**

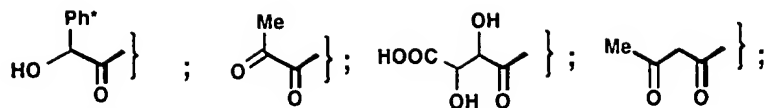


**X =** OH, OAc, NH<sub>2</sub>, NHCbz, OMe, CN, NO<sub>2</sub>, F, Cl, Br, and disubstituted benzoates with a combination of these groups 'X'.

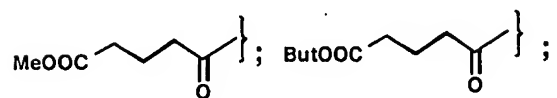
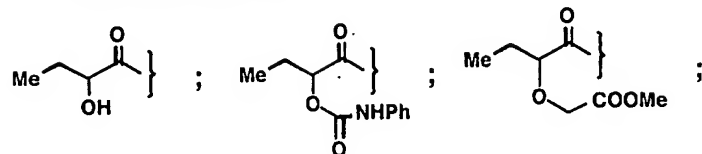


**n = 1 to 4**



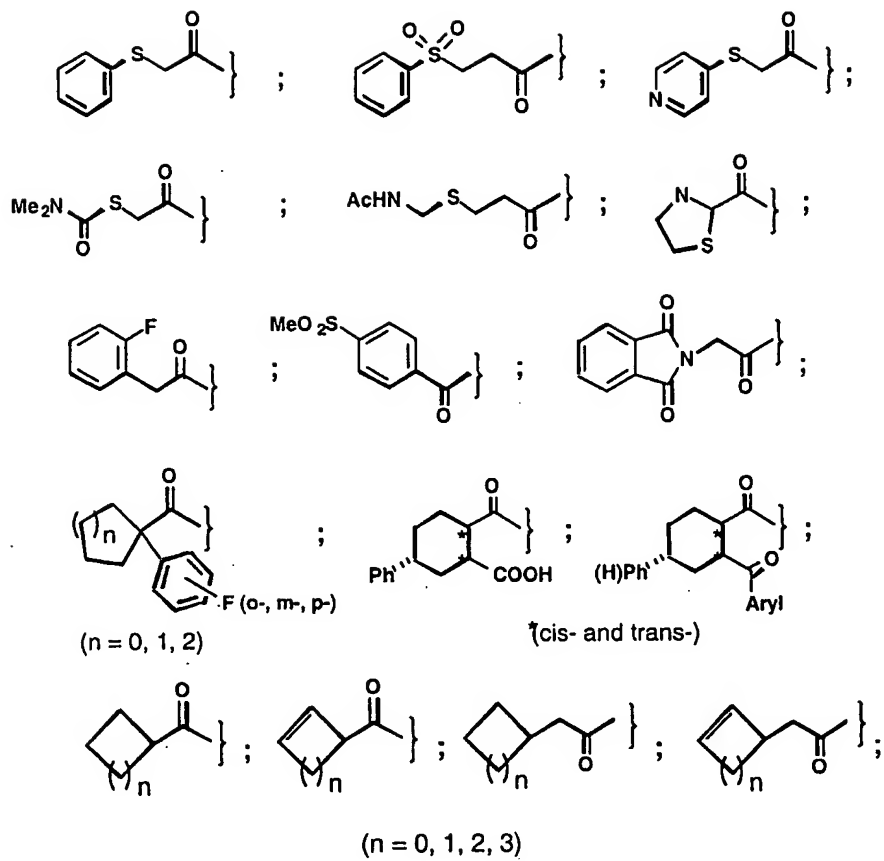


\*(and substituted Ph)

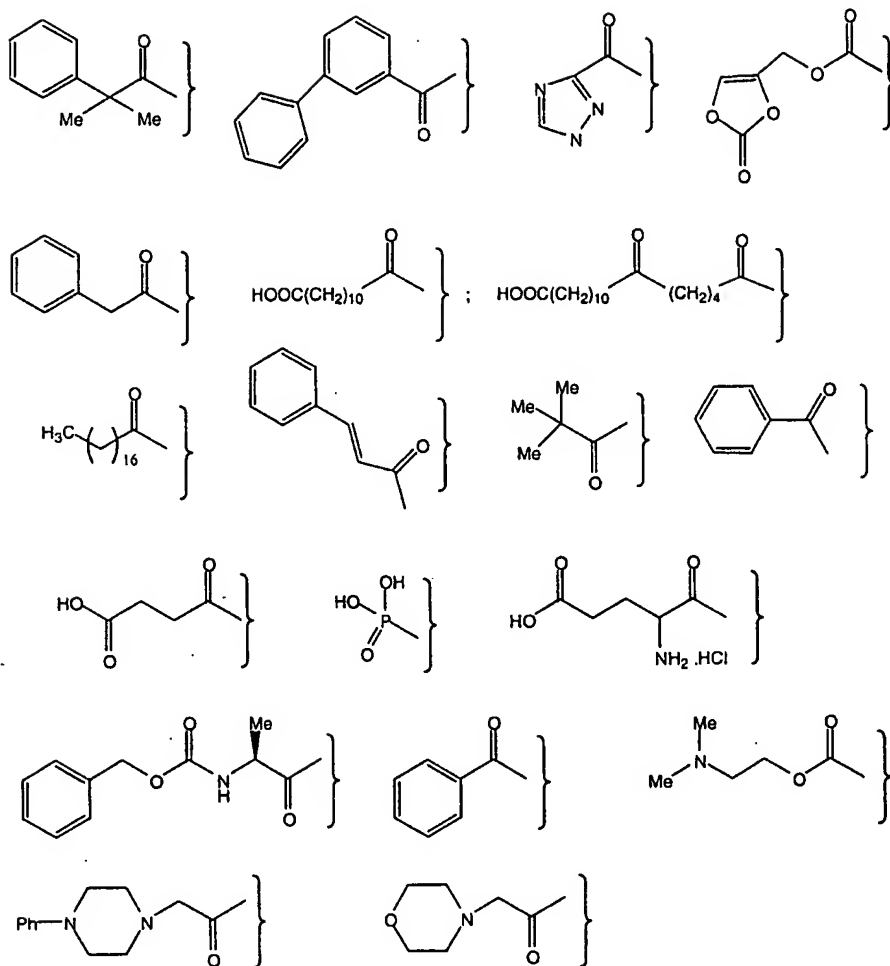


(and 5'----> 3' cyclic diester)



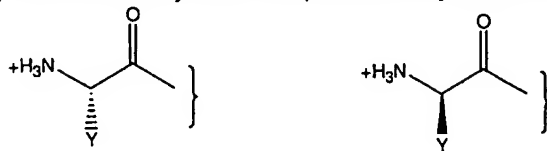




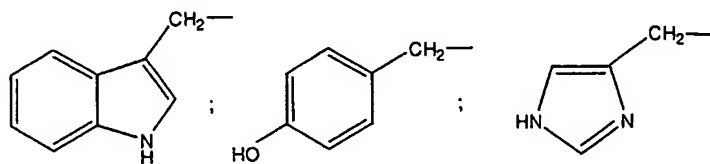




$R^{2a}CO$ ,  $R^{3a}CO$ , and  $R^{5a}CO$  may also be represented by the formulas:

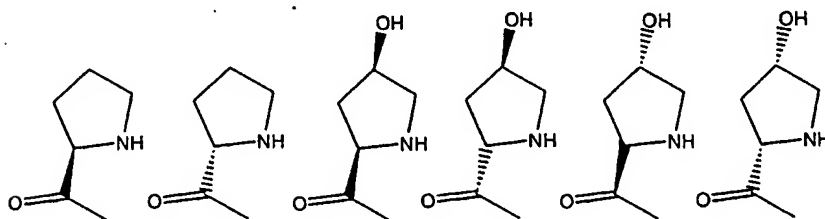


$Y = H, CH_3; CH_3CH_2^-; CH_3CH_2CH_2^-; Me_2CH^-; Me_2CH_2CH_2^-; CH_3CH_2CH(Me)-$   
 $PhCH_2^-; HOOCCH_2CH_2^-; HSCH_2^-; HOOCCH_2^-; MeSCH_2CH_2^-; HOCH_2^-;$



or  $Y$  is  $H_2N(CH_2)_4-$  or  $CH_3CH(OH)-$ ; or a pharmaceutically acceptable salt thereof;

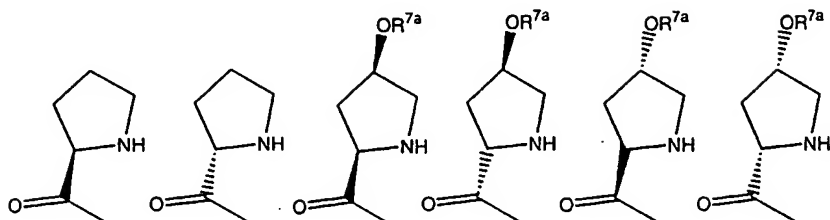
or  $Y$  taken together with the  $\alpha$  carbon and N form



5 or a pharmaceutically acceptable salt thereof.



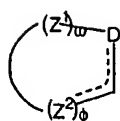
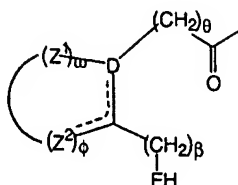
or Y taken together with the  $\alpha$  carbon and N form



wherein R<sup>7a</sup> is as defined above;  
or a pharmaceutically acceptable salt thereof.



Exemplary 5'-heteroaryl esters of Formulas I & II wherein  $R^5 =$



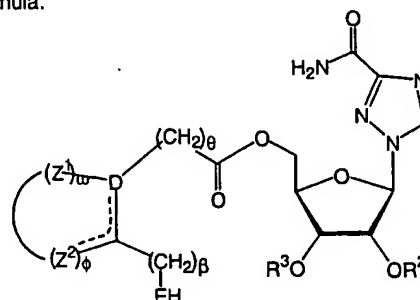
represents a heteroaryl ring of 5-7 total atoms at maximum unsaturation wherein: D = C, or when  $\theta > 0$  is N or S

E = O or NH

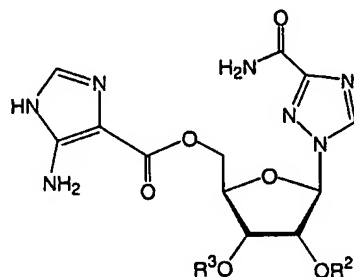
$Z^1$  and  $Z^2$  = independently -C(H)=, -C(H)=N-, -N=, -N(H)-, S, S-C(H)= or S-N=

$\theta$  and  $\beta$  = independently 0, 1, or

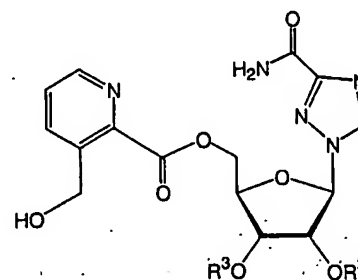
$\omega$  and  $\phi$  = independently 1, 2, or 3. The 5'-ester of formula is represented by the formula:



The following 5' esters may be prepared as described in Schemes hereinabove, using appropriately protected acids which are readily obtained by procedures well known to one skilled in the art.



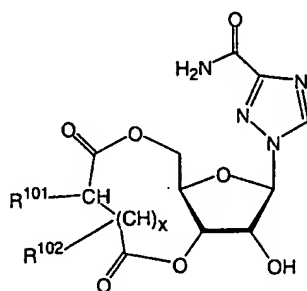
D = C, E = NH,  $Z^1 = (-CH=N-)$ ,  $\omega = 1$ ,  
 $Z^2 = -NH-$ ,  $\phi = 1$ ,  $\theta = 0$ , and  $\beta = 0$



D = C, E = O,  $Z^1 = (-CH=N-)$ ,  $\omega = 1$ ,  
 $Z^2 = -CH=$ ,  $\phi = 2$ ,  $\theta = 0$ , and  $\beta = 1$

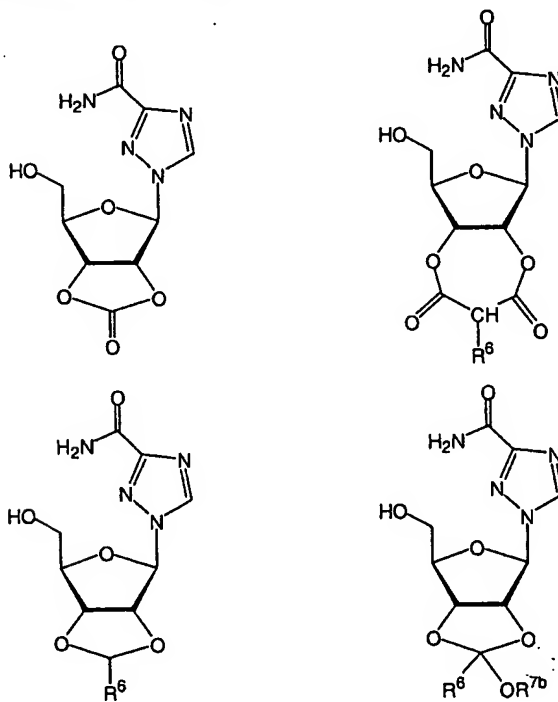


The following 5'-3' cyclic ester (Formula I wherein  $R^2=H$ ) may be prepared using the Schemes herein above and readily available starting materials.



wherein  $R^{101}$  and  $R^{102}$  are independently H, alkanoyloxy,  $OR^{7b}$  or  $NR^6R^{7b}$  and  $x=1$  or  $2$

The following 3'-2' cyclic esters (formula I wherein  $R^5=H$ ) may be made using the Schemes herein above and readily available starting materials.

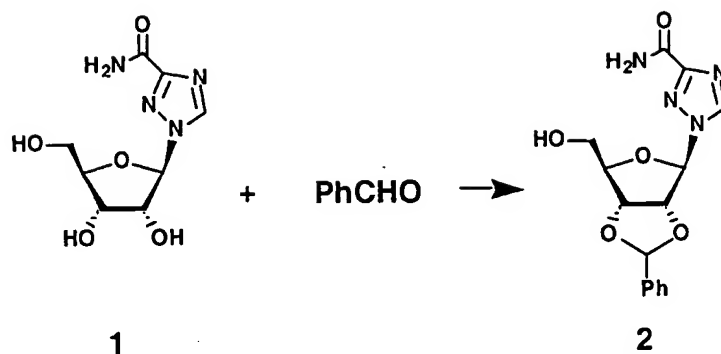




5

Example I

A.



10

A.-Benzylidene ribavirin

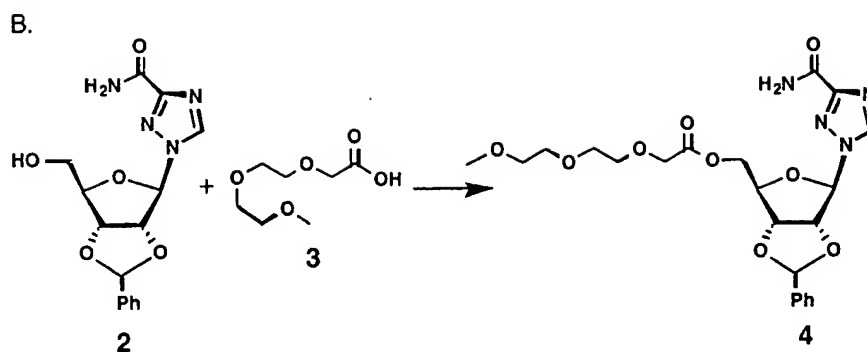
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Combine 20 g ribavirin (1, 87 mmol), 200 ml of benzaldehyde, and 20 g of  $\text{ZnCl}_2$ . Stir the so-formed reaction mixture at ambient temperature for 24 hours. Pour the resulting solution, with stirring, into 2.5 L of ethyl ether ( $\text{Et}_2\text{O}$ ). Suction-filter the resulting mixture and dry the solid precipitate. Mix the solid precipitate with 1.2 L of ice-cold 2N sodium hydroxide (NaOH) solution. Extract the mixture with 2x0.75L of cold ethyl acetate (EtOAc) and wash the organic layer with brine. Gravity-filter the organic layer through fluted filter paper, then concentrate it in vacuo to leave a solid. Triturate the solid thoroughly with 0.5 L of  $\text{Et}_2\text{O}$ , suction-filter and wash the so-formed precipitate with fresh  $\text{Et}_2\text{O}$  to leave 23 g of compound 2 as a solid; Calc. for  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_5$  (332.32). MS(FAB) = 333.1.

25





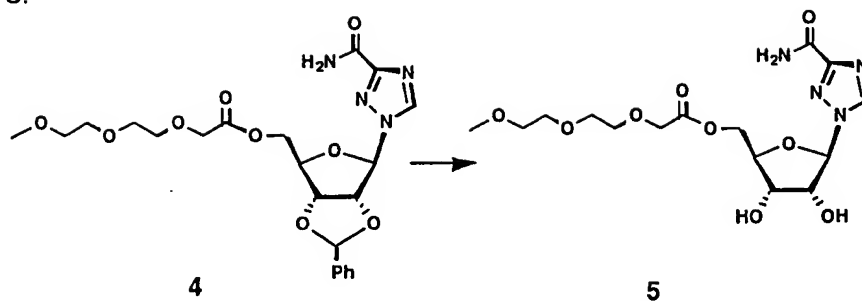
- 5
- 10 Combine 0.5g (2.8 mmol) of compound 2 from step A, 0.80g (2.4 mmol) of compound 4  
 [MeO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H] and 0.8 g (1.2 mmol) of 4-(N,N-dimethylamino)pyridine  
 (DMAP) in 15 ml of N,N-dimethylformamide (DMF). Add 2.5 ml of a 1M solution of  
 dicyclohexylcarbodiimide (DCC) in dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), and stir the resulting  
 mixture at ambient temperature for 0.5 hour. Heat the so-formed reaction mixture at 100  
 15 °C for 1 hour. Quench the reaction mixture with aqueous 5% KH<sub>2</sub>PO<sub>4</sub>, and extract it  
 with 2x100 ml of ethyl acetate (EtOAc). Wash the organic extract with 20 ml cold water,  
 then with saturated brine. Gravity-filter the organic extract through fluted filter paper,  
 then concentrate the filtrate *in vacuo* to leave a gum residue. Purify the residue by  
 column chromatography (silica gel, gradient of 1% to 6% methanol-CH<sub>2</sub>Cl<sub>2</sub>) to give 0.48  
 20 g of compound 4; Calc. for C<sub>22</sub>H<sub>28</sub>N<sub>4</sub>O<sub>9</sub> (492.49); MS(FAB) = 493.1.

25

30



C.



10

C. Treat 0.45 g 4 (0.91 mmol) with 10 ml of trifluoroacetic acid (TFA)-water (9:1 v/v) at ambient temperature for 0.5 hour. Quench with 30 ml xylene, then concentrate the so-formed mixture *in vacuo* to leave a gum. Triturate the gum with EtOAc, dilute with Et<sub>2</sub>O, then suction-filter and dry the gum to leave 0.23 g of compound 5 as a solid, Calc.

15

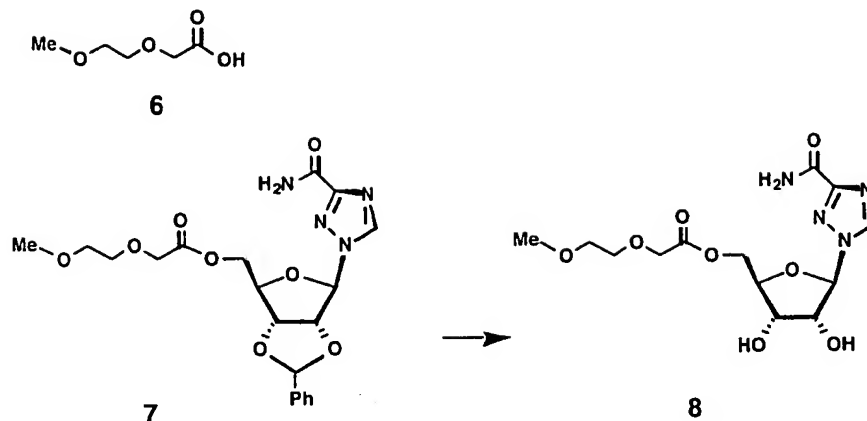
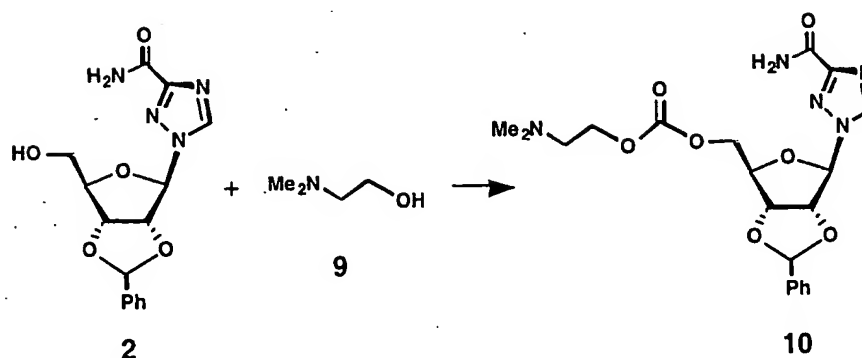
C<sub>15</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub> (404.38); MS(FAB) = 405.1.

### Example 2

Follow the procedures of Example 1A and 1B except substitute an equivalent amount of the compound 6 (MeOCH<sub>2</sub>CH<sub>2</sub>OCHCO<sub>2</sub>H) for compound 3 in step B to form compound 8. Follow the procedures of step C of Example 1 except substitute an equivalent amount of compound 7 for compound 4 to form the compound 8.

20

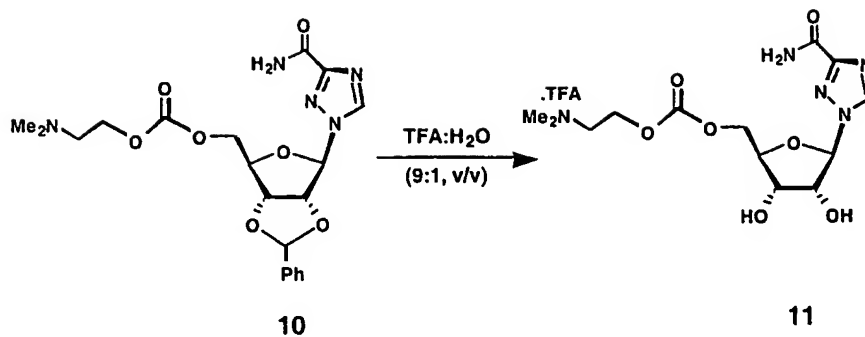


Example 3

- A. Treat a solution of 0.32 g (3.6 mmol) of compound 9 [2-(N,N'-dimethylamino)ethanol] in 10 mL of N,N-dimethylformamide (DMF) at 5°C with 0.58 g carbonyldiimidazole (3.6 mmol), and allow the so-formed solution to warm to 20°C over 0.5 hr. Add to the resulting reaction mixture 0.8 g (2.4 mmol) of compound 2 prepared in accordance with Example 1A and stir the so-formed reaction mixture at ambient temperature for 24 hr. Concentrate the mixture *in vacuo*, add 50 mL of ethyl ether, and allow the so-formed mixture to set for 24 hr. Decant the supernatant solution, and purify the residue by column chromatography (silica gel, gradient of 10% to 20% methanol-tetrahydrofuran) to give 0.21 g of compound 10; calc.  $C_{20}H_{25}N_5O$ , (447.44). MS(FAB) = 448.1.

B

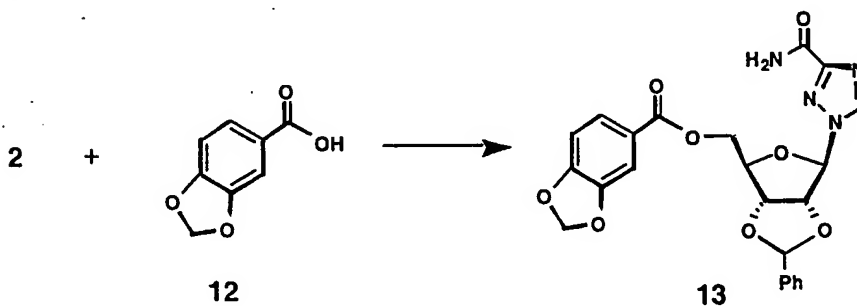




Follow the procedures of Example 1C except substitute an equivalent amount of  
 5 compound 10 for compound 4 to obtain compound 11.

#### Example 4

10 A.

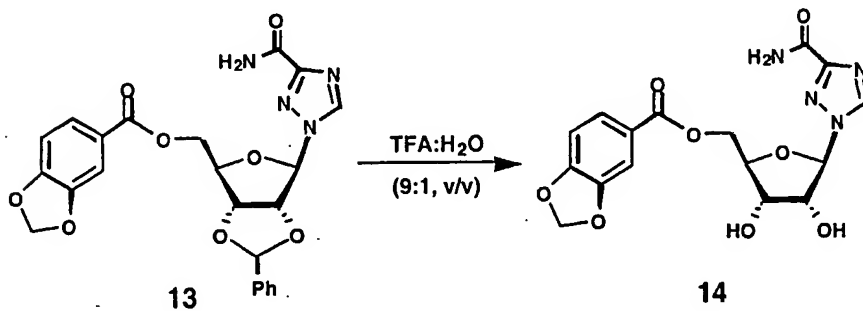


A stirred, dry DMF (5mL) solution of 500 mg (1.506 mmol) of compound 2  
 15 prepared in accordance with the procedures of Example 1A, 300 mg (1.2 eq) of  
 piperonylic acid (compound 12) was treated at ambient temperature with 732 mg (1.1eq)  
 of benzotriazolyloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP  
 reagent") and 576 $\mu$ L (2.2 eq) of Hunig's base, i.e., -diisopropylethyl amine,  
 [(i-Pr)<sub>2</sub>NEt], under a nitrogen atmosphere. The so-formed reaction mixture was stirred  
 20 overnight at ambient temperature. Thin layer chromatography (TLC) showed one major  
 new spot. The reaction mixture was quenched with an aqueous NH<sub>4</sub>Cl solution and



diluted with EtOAc. The organic layer was washed with water and brine and then dried over  $\text{Na}_2\text{SO}_4$ . The organic solvent was evaporated to produce a crude purple solid. The crude solid was purified on a silica gel chromatography column with 2-3%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  as an eluent. The appropriate fractions were combined to give 550 mg of compound 13 as a purple-tinted solid (76% yield). The  $^1\text{H}$  nmr spectrum (350 MHz in  $\text{CDCl}_3$ ) was consistent with the structure of 13.

B.



10

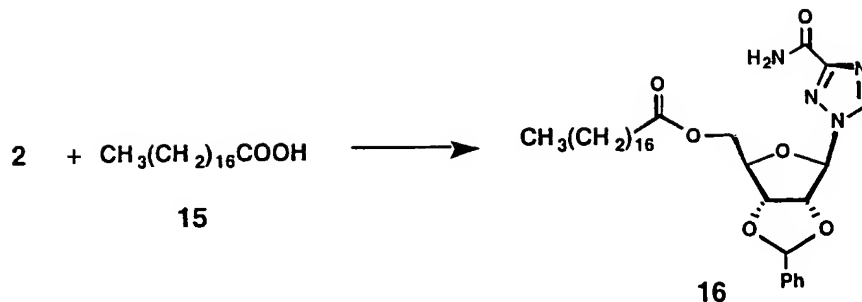
Compound 13 from step A was treated with 4 mL of TFA:H<sub>2</sub>O (9:1, v/v) for 40 min. at ambient temperature. The solvents were evaporated to give a yellow solid. Water was added and evaporated. The crude solid was dried overnight. To the crude product was added 2 x 4 mL of MeOH. The MeOH layer was yellow. The insoluble material was collected and dried to give 342 mg of compound 14 as a white solid. The  $^1\text{H}$  nmr spectrum was consistent with the structure of 14.

15



**Example 5**

A.

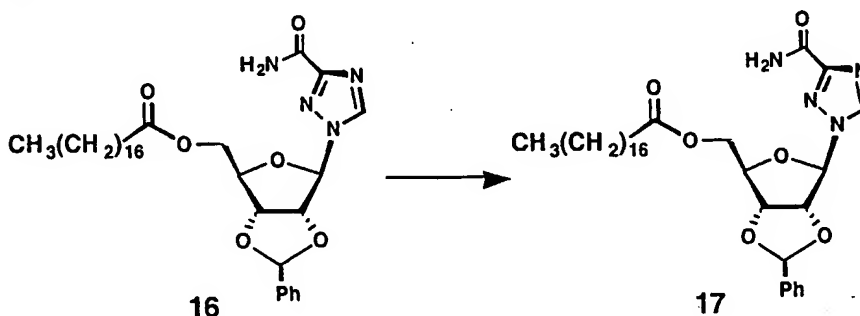


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To a stirred solution of 500 mg (1.505 mmol) of 2 prepared in accordance with Example 1A in 3 mL of dry DMF at ambient temperature was added 516 mg (1.2 eq) of stearic acid (compound 15), 670 mg (1.0 eq) of the BOP reagent and 792  $\mu\text{L}$  (3.0 eq) of Hunig's base. The so-formed reaction mixture was stirred overnight at ambient temperature. The reaction mixture was isolated in accordance with the procedures of Example 4A to give 595.5 mg of compound 16 as a viscous white solid (66% yield). The  $^1\text{H}$  nmr spectrum was consistent with the structure of 16.

15 B.



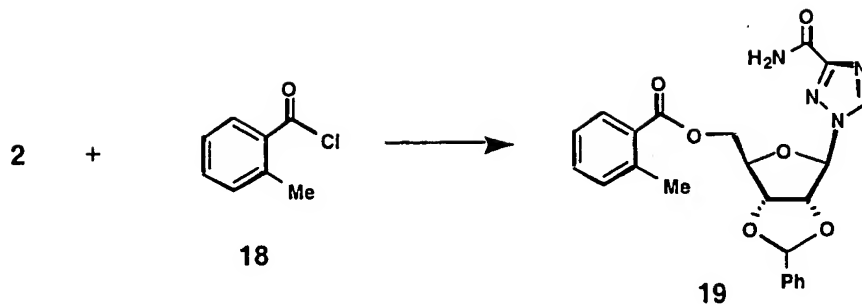
Compound 16 (417 mg, 0697 m mol) was treated in accordance with the procedures of Example 4B to give 330 mg of compound-17 as a white solid (93% yield). The  $^1\text{H}$  nmr spectrum and MS-FAB were consistent with the structure of 17.

20

**Example 6**

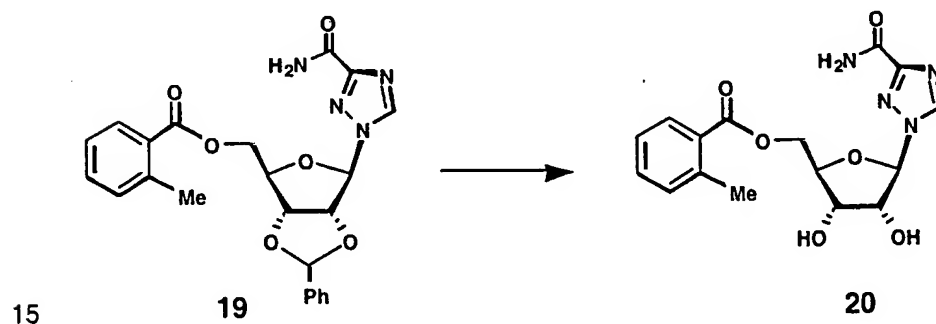


A.



- 5 To a stirred suspension of 332 mg (1.0 mmol) of compound 2 prepared in accordance with Example 1A in 5 ml of dry  $\text{CH}_2\text{Cl}_2$  was added 209  $\mu\text{L}$  (1.5 eq) of triethylamine ( $\text{Et}_3\text{N}$ ) and 167  $\mu\text{L}$  (1.2 eq) of o-toluoyl chloride (compound 18). TLC showed completion of the reaction after the reaction mixture had been stirred at ambient temperature for 4 hours. The so-formed clear reaction mixture was diluted with EtOAc and quenched with water.
- 10 The separated organic layer was washed with water and brine, dried and evaporated to give a crude white solid. The crude solid was purified on silica gel column chromatography eluting with 2-3% MeOH to give 262 mg of compound 19 as a white solid (57% yield).

B.

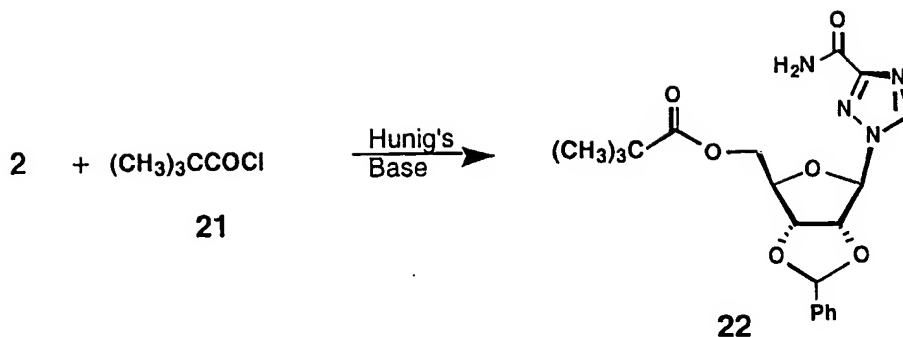


Compound 19 (262 mg) was treated with 3 mL of TFA: $\text{H}_2\text{O}$  (9:1 v/v) in accordance with the procedure of Example 4A to give 210 mg (99% yield) of the compound 20. The  $^1\text{H}$  nmr spectrum was consistent with the structure of compound 20.



Example 7

A.



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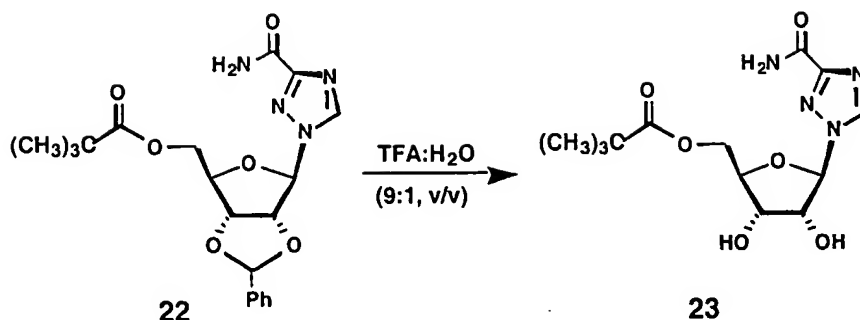
20

To a stirred suspension in a reaction flask immersed in an ice bath of 498 mg (1.5 mmol) of 2 prepared in accordance with Example 1A in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, was added 146  $\mu$ L (1.80 mmol, 1.2 eq) of pyridine and 203  $\mu$ L (1.65 mmol, 1.1 eq) of trimethylacetyl chloride (compound 21) at 0°C. The ice bath was removed after 5 min. Stirring was continued for 30 min. and 1 mL of DMF was added; the mixture changed from a suspension to a cloudy solution. By TLC, there was a substantial amount of unreacted starting material (compound 2). The reaction mixture was stirred overnight, and an additional amount of compound 21 (203  $\mu$ L, 1.1 eq) and 180 mg (1.5 eq) of DMAP were added. The so-formed reaction mixture was stirred for 4 days at ambient temperature.

There was still some unreacted starting material (compound 2) by TLC. The reaction mixture was worked-up by routine extraction between H<sub>2</sub>O/EtOAc. The crude product was purified by silica gel column chromatography eluting with 2-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give 411.3 mg of compound 22 (66% yield) as a white solid.

B.



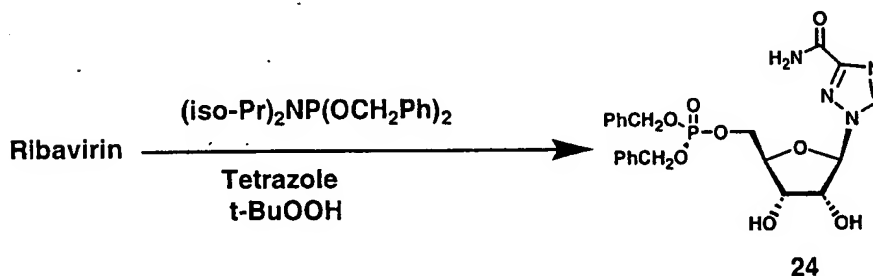


Compound 22 (316 mg) was treated with 4 mL of TFA:H<sub>2</sub>O (9:1 v/v) in accordance with the procedures of Example 4B to give 265 mg of compound 23.

5

### Example 8

A.



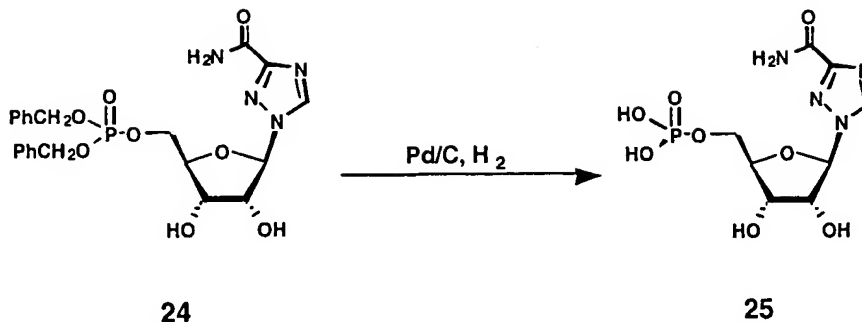
To a stirred mixture of 500 mg (2.1 m mol) of ribavirin and 2.07 g (1.04 mL, 1.5 eq, 3.1 mmol) of N,N-disopropyl-dibenzyl phosphoramidate in 5 mL of DMF at room temperature, was added 433 mg (6.1 m mol, 3 eq) of tetrazole. The resulting reaction mixture was stirred at room temperature for 2 hrs. , and then 1.11 mL (3 eq) of tert-butylperoxide (5.5M in decane) were added. The so-formed reaction mixture was stirred for 2 hrs. Water was added and the organic layer was washed, dried and evaporated to give a crude product. The crude product was purified on silica gel column chromatography using MeOH/CH<sub>2</sub>Cl<sub>2</sub> as an eluent to give 493 mg of compound 24 as white solid.

FAB:MS:MH<sup>+</sup>=505.2.

15

B.

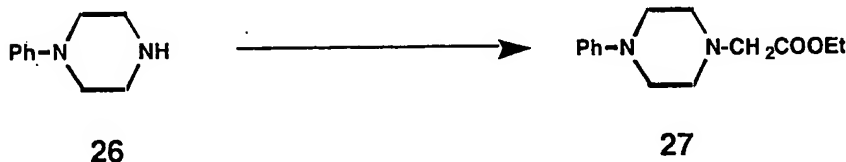




A suspension of compound 24 (278 mg) in a mixture of 3 mL of MeOH and 3 mL of water and 150 mg of 10% Pd on carbon was placed under an atmosphere of hydrogen for 4 hrs. The suspension was filtered through a pad of celite and the solid was washed thoroughly with MeOH. The combined filtrates were concentrated under reduced pressure to give 169.3 mg of the compound 25 as a white solid. FAB-MS,  $MH^+ = 325.1$

#### Example 9

A.

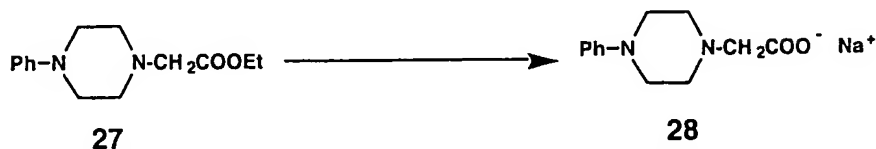


An oil dispersion of NaH (0.88g of NaH, 0.022 mmol, 1.1 eq) was washed once with dry hexane and then suspended in 10 mL of dry THF. Compound 26 (N-phenylpiperazine, 3.24g, 20mmol) was added to the reaction vessel containing NaH in dry THF immersed in an ice bath. The ice bath was removed and the so-formed reaction mixture was stirred for 1 hr. at room temperature. To the stirred white reaction mixture was added 2.66 mL (0.024 m mol, 1.2 eq) of ethyl bromoacetate. The so-formed reaction mixture was stirred overnight. The reaction mixture was cooled to ice bath temperature and quenched with an aqueous  $NH_4Cl$  solution. The so-formed mixture was extracted with EtOAc and the organic layer was washed with aqueous  $NH_4Cl$  brine and dried. The solvent was removed at reduced pressure to provide a crude product which was purified on a silica gel chromatography column using 20% EtOAc/hexane (v/v) as an eluent to



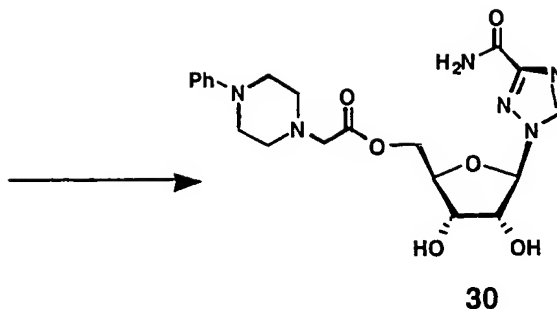
provide 2.10g of compound 27 (ethyl N-phenylpiperazinylacetic acid) as a clear oil. The <sup>1</sup>H nmr spectrum was consistent with the structure of compound 27.

B.





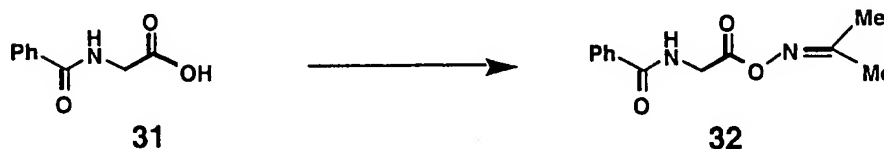
Ribavirin + 29



A suspension of 105.0 mg (0.431 mmol) of ribavirin 237 mg (0.862 mmol) of oxime ester 29 and 0.1 g of Novo SP435 lipase (*Candida antarctica*) in 5 mL of anhydrous THF was stirred at 65°C for 24 hrs. The so-formed reaction mixture was cooled to room temperature, filtered and washed with MeOH. The crude material was purified on silica gel column chromatography using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (v/v) as eluent to produce 66 mg of Compound 30 (a white solid) as a single product (in 42% yield). No other product was observed by TLC. The <sup>1</sup>H NMR spectrum (300 MHz, DMSO-d<sub>6</sub>) was consistent with the 5' ribavirin ester of structure 30.

Example 10

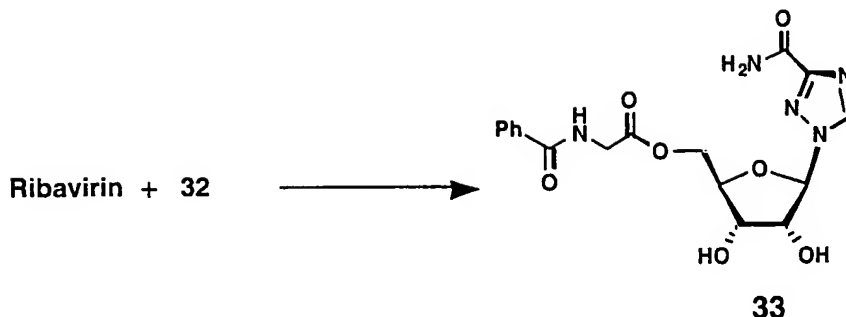
A.



To a stirred solution of 2.45 g (1.4 mmol) of hippuric acid (compound 31) and 1.00 g (1.0 eq) of acetone oxime in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> at room temperature was added 2.83 g (1.0 eq) of DCC. The so-formed reaction mixture was stirred overnight and then filtered. The filtrate was concentrated under reduced pressure to produce a residue which was purified with EtOAc/hexane to give 2.36 g of the acetone oxime ester (32) as a colorless oil. The FAB-MS: MH<sup>+</sup> = 235.1.

B.

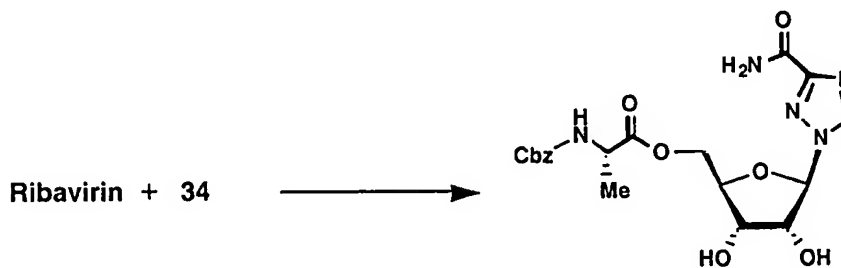




The procedure of Example 9, Step D was used except 2.13 g (9 mmol) of compound 32 was substituted for compound 29, 0.734 g (3 mmol, 1/3 eq) of ribavirin and 0.6 g of SP435 lipase were used in 25 ml of THF. The crude product was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ : MeOH (20:1, v/v) as an eluent to provide a crude product. The crude product was crystallized from MeOH:  $\text{Et}_2\text{O}$  to provide 0.936 g of compound 33. FAB:MS,  $\text{MH}^+ = 406.1$ .

#### Example 11

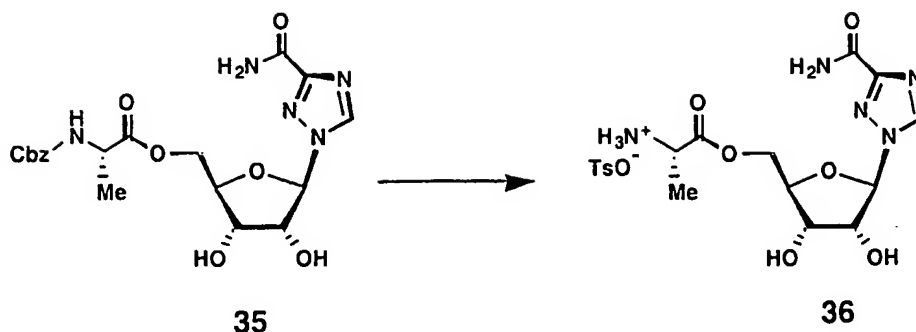
A.



Compound 34, the acetone oxime ester of Cbz-L-alanine, was prepared in accordance with the procedures of F. Morris and V. Gotor, *Tetrahedron*, **1994**, 50, 69-6934 at paragraph bridging 6932-6933. Then, the procedure of Example 10, Step B, was followed using 1.00 g (3.6 mmol) of compound 34 in place of compound 32, 0.294 g (1.2 mmol) of ribavirin, and 0.48 g of Novo SP435 lipase in 12 ml of THF. The crude product was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ : MeOH (20:1, v/v) as an eluent to give 0.660 g of compound 35 as a white solid. The white solid was recrystallized from MeOH-EtOAc to give 0.532 g of compound 35.



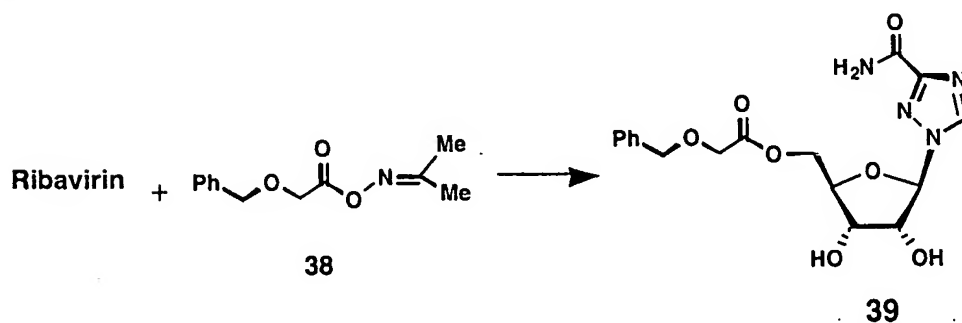
C.



- 5 To a mixture of 0.100 g (0.222 mmol) of compound 35 and 42.3 mg (1 eq) of TSOH.H<sub>2</sub>O in 3 ml of aqueous MEOH was added 50 mg of 10% Pd on carbon. The resulting black suspension was placed under a hydrogen atmosphere for 4 hours. The so-formed reaction mixture was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrates were concentrated and the solvent
- 10 removed to give 0.101 g of compound 36 as a white solid. FAB:MS MH<sup>+</sup>=316.1.

### Example 12

A.



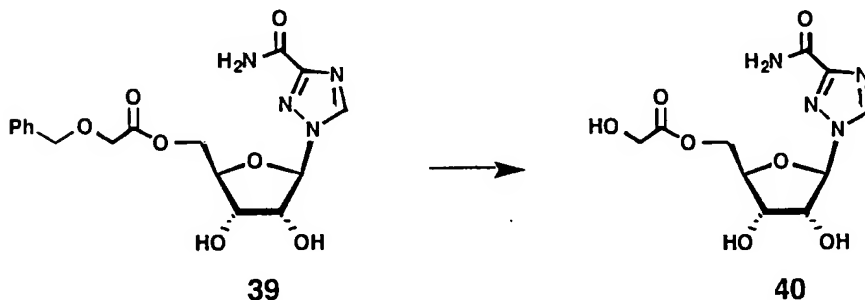
15

Compound 38 (PhCH<sub>2</sub>OCH<sub>2</sub>COO-N=C(CH<sub>3</sub>)<sub>2</sub>) was prepared from 2.17 ml (2.53 eq) benzyloxyacetylchloride (Compound 37) and 1.00 g of acetone oxime in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> containing 1.67 g (1 eq) of DMAP in accordance with the procedure of Example 10 Step A. Then, the procedure of Example 10, Step B was followed using 2.40 g (10.8



mmol) of compound 38 in place of compound 32 1.325 g (5.4 mmol) of ribavirin 2.18 g of Novo SP435 lipase in 70 ml of THF. The mixture was treated overnight at 70°C under a nitrogen atmosphere. The crude product was purified on silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>:MeOH (10:1, v/v) as an eluent to provide 0.511 g of a mixture of two compounds. The desired compound 39 was purified by crystallization from MeOH:Et<sub>2</sub>O to give 0.367 g of compound 39 as a white crystalline product.

B.

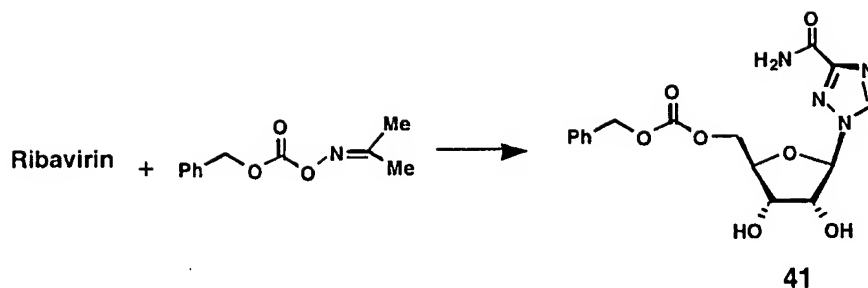


10

To a stirred suspension of 0.200 g of compound 39 in 5 ml of MeOH containing 50 mg of palladium black under an atmosphere of nitrogen was added 0.20 ml of formic acid. The resulting reaction mixture was heated to reflux for 1 hour. The resulting reaction mixture was cooled and filtered through a pad of cotton wool. The solids were thoroughly washed with methanol and then water. The combined filtrates were concentrated under reduced pressure to give a residue. Methanol was added to provide 99.2 mg of the compound 40. FAB-MS:MH<sup>+</sup>= 303.1.

15



Example 13

5

Compound 40 ( $\text{PhCH}_2\text{OCOO-N}=\text{C}(\text{CH}_3)_2$ ) was prepared in accordance with the procedure of Step A of Example 10. Then the procedure of Step B of Example 10 as followed using 500 mg (2.4 mmol) of compound 40 in place of compound 32, 295 mg (1.2 mmol) of ribavirin, 160 mg of Novo SP435 in 15 ml of THF. The so-formed reaction mixture was heated at  $70^\circ\text{C}$  for 3 days. The crude product dissolved in MeOH was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ :MeOH (20:1, v/v) as an eleunt to provide 156 mg of compound 41. FAB:MS,  $\text{MH}^+=379.2$ .

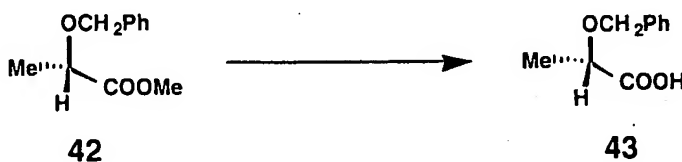
10

Example 14

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A. The benzyl ether of methyl-L-lactate (compound 42) was prepared from methyl-L-lactate in accordance with the procedures of U. Widner Synthesis 1987, 568.

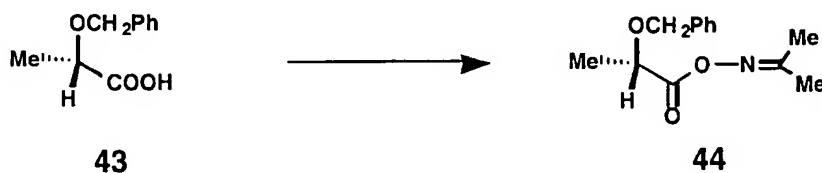
20 B.





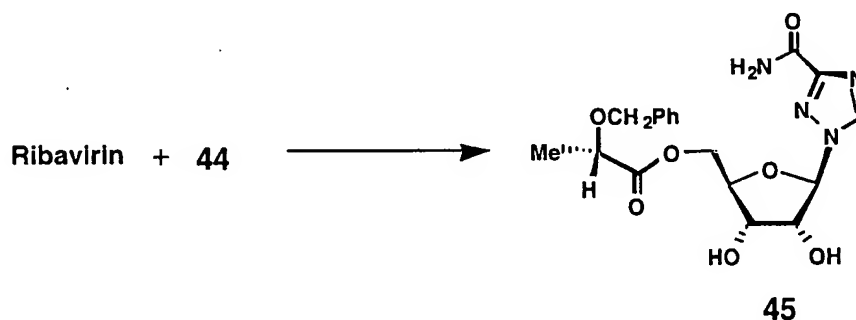
To a stirred solution of 1.00 g of compound 42 in a mixture of 9 ml of MeOH and 3 ml of water was added 216 mg (1 eq) of LiOH.H<sub>2</sub>O. The so-formed reaction mixture was stirred for 4 hours. The resulting mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The aqueous phase was separated, washed with CH<sub>2</sub>Cl<sub>2</sub> and acidified with excess 10% aqueous HCl. The organics were extracted with EtOAc. The EtOAc layer was dried and concentrated to give 779 mg of compound 43 as a colorless oil.

C.



The procedures of Step A of Example 10 were followed using 1.15 g (6.39 mmol) of compound 43 in place of compound 31, 513 mg, (7.03 mmol, 1.1 eq) of acetone oxime, 1.45 g of DCC in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> to produce 1.20 g of the acetone oxime ester, compound 44.

D.

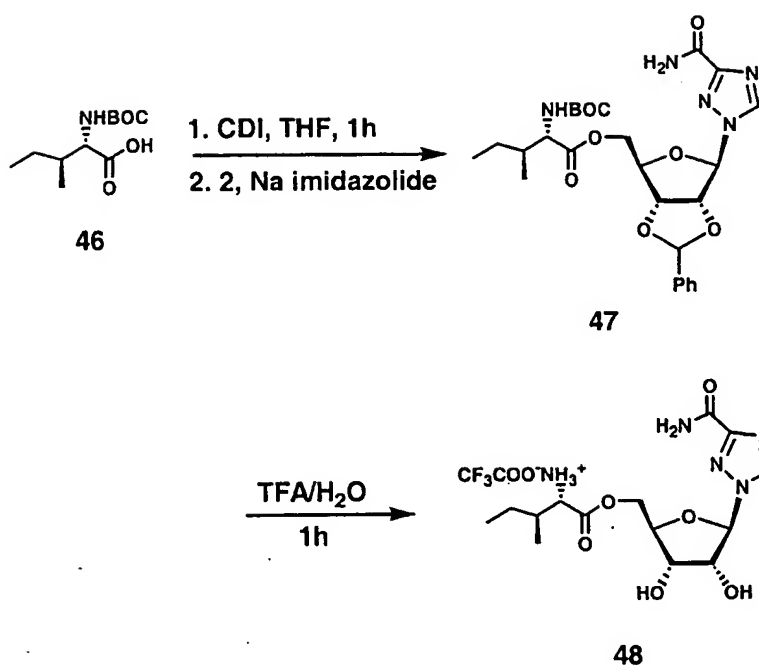


The procedure of Step B of Example 10 was followed using 1.2 g (5.1 mmol) of compound 44 in place of compound 32, 600 mg (2.5 mmol) of ribavirin and 500 mg of Novo SP435 lipase in 20 ml of THF. The mixture washed at 70°C until no starting found by TLC.

The crude reaction product was purified by silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>:MeOH (20:1, v/v) to produce 183 mg of compound 45 as a white solid.



## Example 15



5

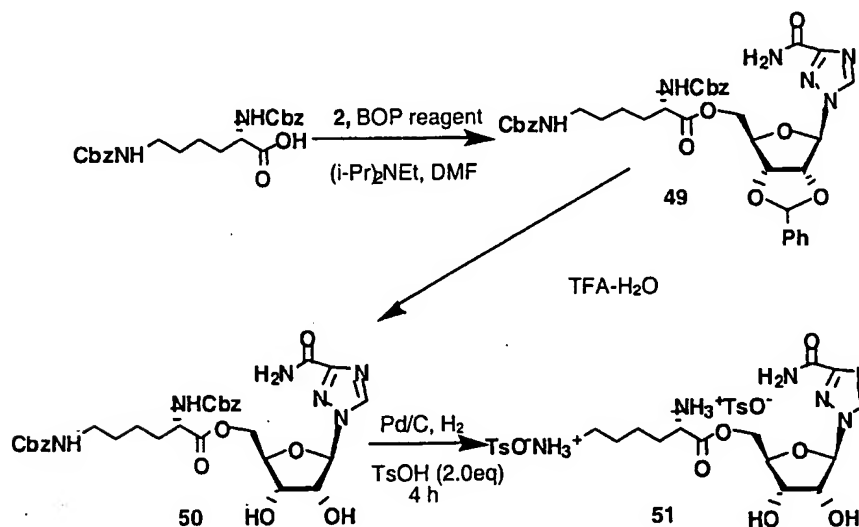
A solution of N-t-Boc-L-isoleucine (available from Sigma Chemical Co. St. Louis, Mo) (1.270 g, 5.5 mmol) in anhydrous THF (30mL) was treated with CDI, i.e., carbonyl-diimidazole (981 mg, 6.05 mmol) at room temperature for 1 hr. The compound 2 of Example 1 (1.660 g, 5.00 mmol) and sodium imidazolidine (150 mg, 1.5 mmol) were then added to the reaction mixture. This mixture was heated at 45°C for 20 hrs. The reaction was diluted with EtOAc and quenched with aqueous NH<sub>4</sub>Cl. The organic layer was washed with water three times and once with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The dried organic layer was filtered and the filtrate was concentrated to give an off white solid which was purified on silica gel column chromatography (5-10% by volume of MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 1.244 g of compound 47.

15



Compound 47 was treated with trifluoroacetic acid (TFA)/ water (9:1 v/v) at room temperature for 1 hr. All volatiles were evaporated. Water was added and evaporated again to afford 1.10 g of compound 48 as a soft solid. MS(FAB)=358 (MH<sup>+</sup>, 100%).

5

Example 16

A solution of N,N-diCbz-L-lysine (available from Sigma Chemical Co. St. Louis, Mo) (749 mg, 1.81 mmol) and compound 2 (500 mg, 1.506 mmol) in anhydrous DMF (5 mL) was treated with (732 mg, 1.66 mmol) of benzotriazolyloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP reagent" available from Sigma Chemical Co. St. Louis, Mo) followed by 576 mL, 3.31 mmol of Hunig's base, i.e., N,N-diisopropyl-ethyl amine, [ "(i-Pr)<sub>2</sub>NEt " available from Aldrich Chemical Co., Milwaukee, WI ] under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and quenched with aqueous NH<sub>4</sub>Cl. The organic layer was washed three times with water, once with brine, and dried over Na<sub>2</sub>SO<sub>4</sub> and . The dried organic layer was filtered and the filtrate was concentrated to give compound 49 as an off white solid .

20

Compound 49 was treated with trifluoroacetic acid/ water (9:1 v/v) at room temperature for 1 hr. All volatiles were evaporated. Water was added and evaporated



again to afford the crude product which was purified on a silica gel column (10 % by volume of MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 520 mg of compound 50 as a white solid.

A solution containing compound 50(140 mg, 0.219 mmol) and p-toluenesulfonic acid monohydrate, TsOH  $\text{H}_2\text{O}$  (83 mg, 0.438 mmol) was hydrogenated over 10% Pd/C (50 mg) under  $\text{H}_2$  at a pressure of 1 atm for 4 hr. The catalyst was filtered off through a bed of Celite and washed with methanol-water. The filtrate was evaporated to afford 157 mg of compound 51 as a white powder. MS(FAB)= 373 ( $\text{MH}^+$ , 100%).

#### Example 17

10

Follow the procedures of Examples 11, 15 or 16 except substitute an equivalent amount of the Cbz- or Boc-D- amino acid derivative of the amino acid listed in the left hand column in the Table 3 below for the Boc-L-isoleucine used in Example 15, or the diCbz-L-lysine used in Example 16, or the Cbz-L-alanine used in Example 11 to obtain the compounds of formula I or a pharmaceutical acceptable salt thereof wherein the R is the moiety listed in Table AA herein above

15

#### Example 18

20

The polyethylene glycol conjugates listed in the right hand column of the Table BB below. can readily be prepared and their molecular weight determined by one skilled in the art view of known methods such as described in European Patent Applications EP0236987 , EP0510356 and. EP 0 809 996 as well as U.S.Patent No. 5,642,575.

25 The starting polyethylene glycols (PEG) and PEG monomethyl ethers of various molecular weights e.g. 750, 1900, 5000, 10,000 can readily be prepared by methods known in the art or can be obtained from commercial sources. The activated polyethylene glycol conjugates listed in the left hand column of the Table BB below can readily be prepared and their molecular weight determined by one skilled in the art

30 view of known methods such as described in European Patent Applications EP 0 236 987, EP 0 510 356 and. EP 0 809 996 as well as U.S.Patent No. 5,642,575 .to obtain the compounds of formula I or a pharmaceutical acceptable salt thereof wherein the R is the moiety listed in the right hand column of the Table BB below:

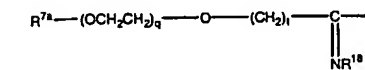
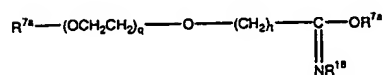
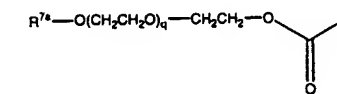
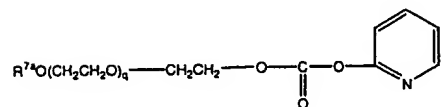
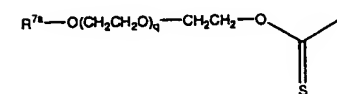
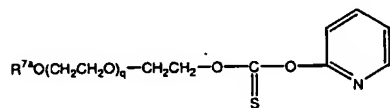
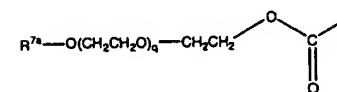
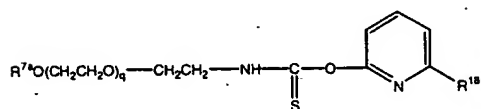
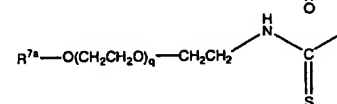
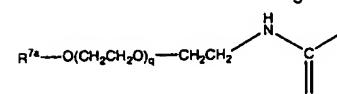
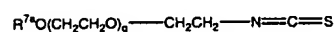
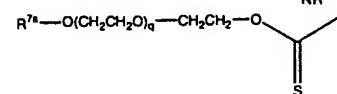
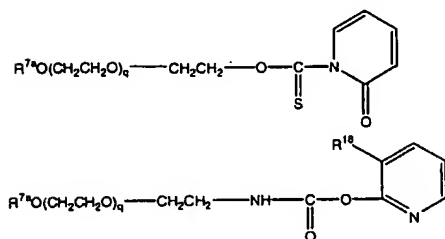
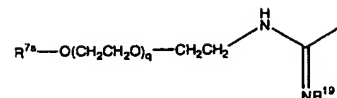
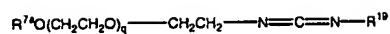


TABLE BB

## COLUMN A

## COLUMN B

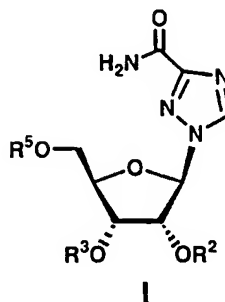
5





CLAIMS:

1. A compound represented by formula I



5

- wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^2$ ,  $R^3$  or  $R^5$  is H,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$  and wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is not H; wherein  $R^6$  is H, alkyl, alkanoyl, aryl, heterocyclic, cycloalkyl,  $NR^{7a}R^{7b}$ , alkenyl, or alkynyl; or  $R^6$  is alkyl, alkanoyl, alkenyl or alkynyl substituted by halo, phenyl, cycloalkyl,  $NR^{7a}R^{7b}$ , hydroxy, or alkoxy;
10. 15

or  $R^6$  is aryl substituted by phenyl; halo, CN,  $NO_2$ , OH,  $R^{18}$ ,  $CF_3$ , SH,  $SR^{7a}$ ,  $SOR^{7a}$ ,  $SO_2R^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $CO_2H$ ,  $CO_2^-$ ,  $OR^{7a}$ ,  $O^-M^+$  or  $S^-M^+$  wherein  $M^+$  is an alkali metal,

20

W is O,  $NR^{18}$  or S;

$R^{7a}$  is H, alkyl, alkanoyl, or aryl; or  $R^{7a}$  is alkyl, alkanoyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

- 25 and  $R^{7b}$  is H, alkyl or aryl or  $R^{7b}$  is alkyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

or  $R^{7a}$  and  $R^{7b}$  taken together with N and one of  $CHR^{7a}$ ,  $NR^{7a}$ , O, S, SO or  $SO_2$  form a five-, six- or seven- membered ring;

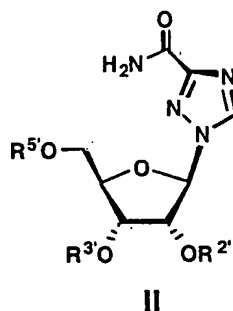


$R^{17}$  is H,  $OR^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$ ;  
 $R^{18}$  is H, alkanoyl or alkyl;  
 and  $x = 0$  or  $1$ ;

5

or a pharmaceutically acceptable salt thereof.

2. A compound represented by formula II

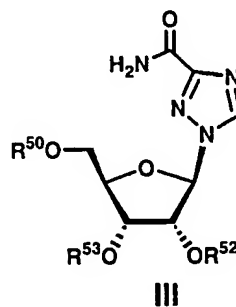


10

wherein at least one of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a natural or unnatural  $\alpha$ -amino acid residue; or a pharmaceutically acceptable salt thereof.

15

3. A compound represented by formula III

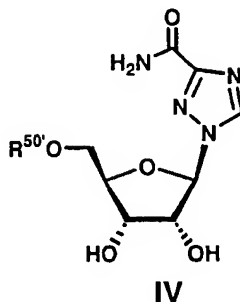


wherein at least one of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  is a straight or branched chain polyalkylene oxide polymer conjugate; and the remaining two of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  are independently H or a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof

20



4. A compound represented by the formula IV



5

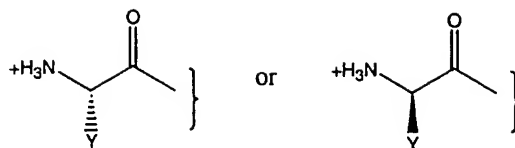
wherein R<sup>50'</sup> is a straight or branched chain polyalkylene oxide polymer conjugate; or a pharmaceutically acceptable salt thereof

10

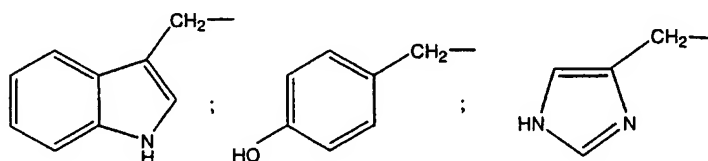
5. The compound of claim 1 wherein R<sup>2</sup> or R<sup>3</sup> is a natural or unnatural  $\alpha$ -amino acid residue or the compound of claim 2 wherein R<sup>2'</sup> or R<sup>3'</sup> is a natural or unnatural  $\alpha$ -amino acid residue; the natural or unnatural  $\alpha$ -amino acid residue being represented by the formula:

15



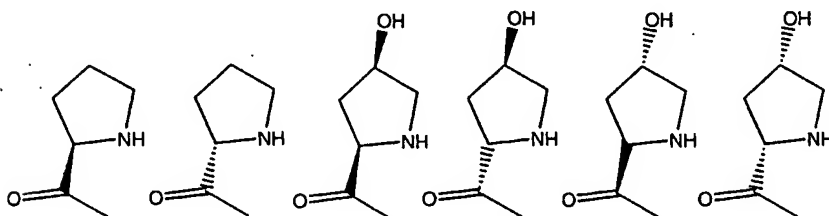


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



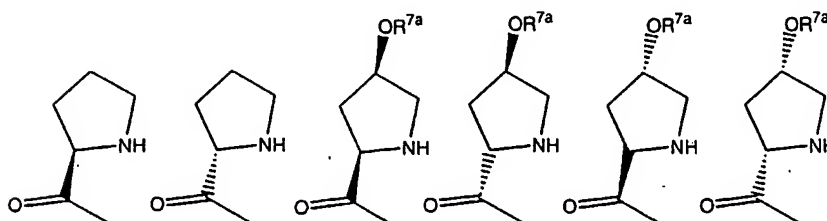
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)- or a pharmaceutically acceptable salt thereof;

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.



4. The use of a compound of any preceding claim for the manufacture of a pharmaceutical composition for treating patients having chronic hepatitis C infection to eradicate detectable HCV-RNA
5. The use of a compound of any preceding claim and a interferon-alpha for the manufacture of a pharmaceutical composition for treating patients having chronic hepatitis C infection to eradicate detectable HCV-RNA ;  
or a pharmaceutically acceptable salt thereof.
6. The compound, pharmaceutical composition or use of any preceding claim (a) wherein  $R^2 = R^3 = H$ . or wherein  $R^{2'} = R^{3'} = H$ ; or (b) wherein  $R^2 = R^5 = H$ . or wherein  $R^{2'} = R^{5'} = H$ ; or (c). wherein  $R^3 = R^5 = H$ . or wherein  $R^{3'} = R^{5'} = H$
7. The compound, pharmaceutical composition or use of any preceding claim wherein (a) at least one of  $R^2$ ,  $R^3$  or  $R^5$  in claim 1 or (b) at least one of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  in claim 2; or (c) at least one of  $R^{52}$ ,  $R^{53}$  or  $R^{50}$  in claim 3; or (d)  $R^{50'}$  in claim 4 is one of
- $R^{7a}-OCH_2CH_2(OCH_2CH_2)_q-(W)_x-CO-$ ,
- $R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-(W)_x-CO-$ ,
- $R^{7a}(OCH_2CH_2)_q-O-(CH_2)_l-C(=NR^{18})-$
- $R^{7b}OOC-(CH_2)_m-[CR^{7a}(OR^{7a})]_n-(W)_x-CO-$ ,
- $R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-CO-$
- $R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$
- $R^{7b}OOC-(CH_2)_m-(OCHR^{7a})_n-(W)_x-CO-$ , or
- $R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-CO-$
- $R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$ ; and



$W = -O-$  or  $-NR^{18}-$ ; and  $R^{18} = H$ ;

$m = 0$  to  $100$ ;  $n = 0$  to  $6000$ ;  $t = 1$  to  $4$ ; and  $q = 1$  to  $5000$ .

- 5 10. The compound, pharmaceutical composition or use of any preceeding claim wherein  $R^2 = R^3 = H$ ; or wherein  $R^{2'} = R^{3'} = H$ ; and  $R^5$  or  $R^{5'}$  or  $R^{50}$  or  $R^{50'}$  is one of  $R^{7a}-OCH_2CH_2(OCH_2CH_2)_q-(W)_x-CO-$ ;

$R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-(W)_x-CO-$ ,

10  $R^{7a}-(OCH_2CH_2)_q-O-(CH_2)_t-C(=NR^{18})-$

$R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-CO-$

15  $R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$

$R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-(W)_x-CO-$ ,

$R^{7b}OOC-(CH_2)_m-[CR^{7a}(OR^{7a})]_n-(W)_x-CO-$ ,

20  $R^{7b}OOC-(CH_2)_m-(OCHR^{7a})_n-(W)_x-CO-$  or

$R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-CO-$

25  $R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$

$W = -O-$  or  $-NR^{18}-$ ; and  $R^{18} = H$ ;

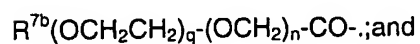
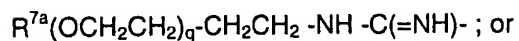
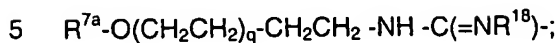
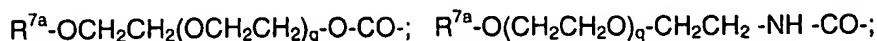
and

30  $m = 0$  to  $100$ ;  $n = 0$  to  $6000$ ;  $q = 1$  to  $5000$ ;  $t = 1$  to  $4$ ; and  $x = 0$  or  $1$ .

11. The compound, pharmaceutical composition or use of any preceeding claim wherein  $R^2 = R^3 = H$  or wherein  $R^{2'} = R^{3'} = H$  and  $R^5$  or  $R^{5'}$  or  $R^{50}$  or  $R^{50'}$  is one of

35  $R^{7b}-OOC-CH_2(OCH_2CH_2)_qOCH_2CO-$ ,  $R^{7a}-OCH_2CH_2(OCH_2CH_2)_qOCH_2CO-$



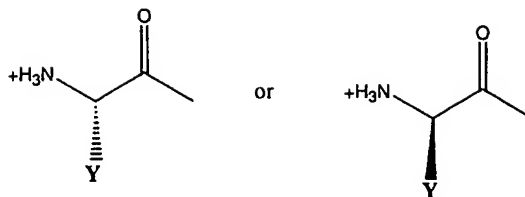


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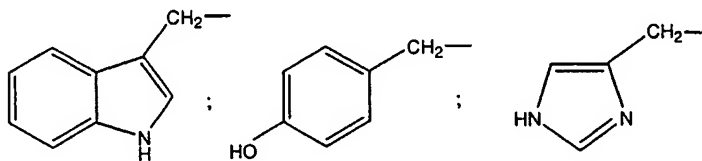
$n = 0 \text{ to } 6000; \text{ and } q = 1 \text{ to } 5000.$

12. The compound, pharmaceutical composition or use of any preceding claim  
 (a) wherein  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate,  
 15 and  $R^3$  or  $R^2$  or is a natural or unnatural  $\alpha$ -amino acid moiety or (b) wherein  $R^5$  is a  
 straight or branched chain polyalkylene oxide polymer conjugate, and  $R^3$  or  $R^2$  is a  
 natural or unnatural  $\alpha$ -amino acid residue and wherein the natural or unnatural  $\alpha$ -  
 amino acid residue is selected from



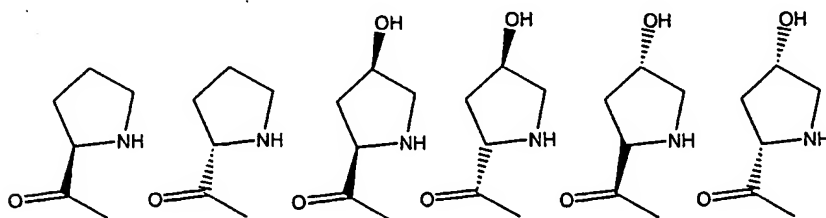


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;

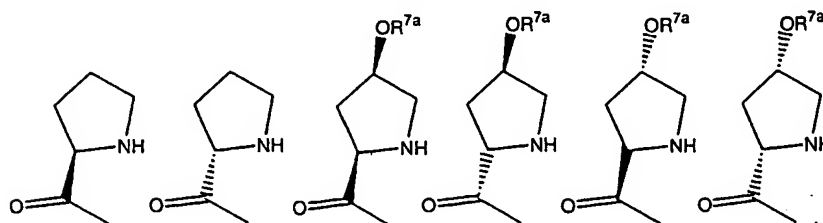


or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)- or a pharmaceutically acceptable salt thereof;

or Y taken together with the a carbon and N form



or form



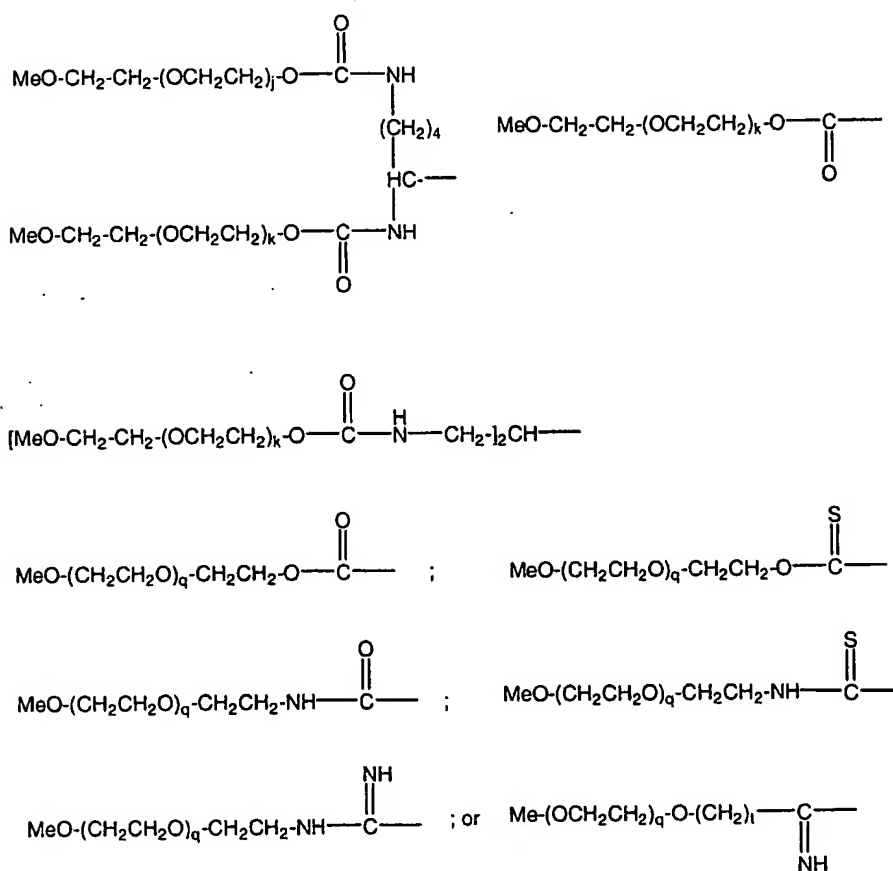
wherein R<sup>7a</sup> is as described herein above;

or a pharmaceutically acceptable salt thereof,



13 The compound of claim 3 or 4 wherein the straight or branched chain polyalkylene oxide polymer conjugate is a straight or branched chain polyethylene oxide polymer conjugate.

14. The compound of claim 13 wherein the straight or branched chain polyethylene oxide polymer conjugates are represented by the formulas ,



10

or a pharmaceutically acceptable salt thereof.



15. The method of treating a patient with a susceptible viral infection which comprises administering to said patient an effective amount of a compound of any preceding claim

5 16. The method of treating a patient infected with chronic hepatitis C which comprises administering to said patient an effective amount of a compound of any preceding claim in association with an effective amount of an interferon alfa for a time sufficient to eradicate detectable HCV-RNA levels,

10 17. The use of any preceding claim, wherein the amount of a compound of any preceding claim administered is from about 1 to about 100 mg per kilogram per day.

15 18. The use of any preceding claim, wherein the interferon-alpha administered is selected from interferon alpha-2a, interferon alpha-2b, a consensus interferon, a purified interferon alpha product or a pegylated interferon-alpha.

19. A pharmaceutical composition comprising a compound of any preceding claim and a pharmaceutically acceptable carrier.

20 20. The use of any preceding claim, wherein the interferon-alpha is selected from interferon alpha-2a, interferon alpha-2b, or a purified interferon alpha product and the amount of interferon-alpha administered is from 2 to 10 million IU per week on a weekly, TIW, QOD or daily basis, and preferably the amount of interferon-alpha administered is 3 million IU TIW.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/21450

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07H19/056 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 21452 A (ADVANCED MAGNETICS INC) 19 June 1997 (1997-06-19) claims 1,2,8; example 28	1-20
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the International search

2 March 2000

Date of mailing of the International search report

10/03/2000

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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 99/21450

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

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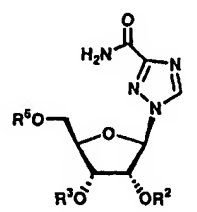
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup>:</b> C07H 19/056, A61K 31/70	<b>A1</b>	<b>(11) International Publication Number:</b> WO 00/23455 <b>(43) International Publication Date:</b> 27 April 2000 (27.04.00)
<b>(21) International Application Number:</b> PCT/US99/21450 <b>(22) International Filing Date:</b> 14 October 1999 (14.10.99) <b>(30) Priority Data:</b> 09/174,059 16 October 1998 (16.10.98) US <b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 09/174,059 (CIP) Filed on 16 October 1998 (16.10.98) <b>(71) Applicant (for all designated States except US):</b> SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07030-0530 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GANGULY, Ashit, K. [US/US]; 96 Cooper Avenue, Upper Montclair, NJ 07043 (US). McCORMICK, Jinping [US/US]; 5 Pace Drive, Edison, NJ 08820 (US). LOVEY, Raymond, G. [US/US]; 65 Woodside Avenue, West Caldwell, NJ 07006 (US). BENNETT, Frank [GB/US]; 419 Draco Road, Piscataway, NJ 08854 (US). SAKSENA, Anil, K. [US/US]; 53 Beverley Road, Upper Montclair, NJ 07043 (US). GIRIJAVALLAB-	<b>HAN, Viyyoor, M. [US/US];</b> 10 Maplewood Drive, Parsippany, NJ 07054 (US). <b>(74) Agents:</b> HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). <b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> RIBAVIRIN-INTERFERON ALFA COMBINATION THERAPY FOR ERADICATING DETECTABLE HCV-RNA IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION		
<div style="text-align: center;"><span style="float: right;">(I)</span></div>		
<b>(57) Abstract</b> <p>Ribavirin derivatives represented by formula (I) wherein at least one of R<sup>2</sup>, R<sup>3</sup> or R<sup>5</sup> is a straight or branched chain polyalkylene oxide polymer conjugate, and pharmaceutical compositions containing them as well as their use to treat patients having susceptible viral infections, alone and in combination with a therapeutically effective amount of interferon-alpha are disclosed.</p>		

\*(Referred to in PCT Gazette No. 34/2000, Section II)



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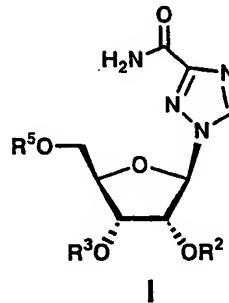
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**RIBAVIRIN-INTERFERON ALFA COMBINATION THERAPY  
FOR ERADICATING DETECTABLE HCV-RNA  
IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION**

**BACKGROUND OF THE INVENTION**

The present invention relates to ribavirin derivatives represented by formula I



wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and pharmaceutical compositions containing them as well as their use to treat patients having susceptible viral infections, alone and in combination with a therapeutically effective amount of interferon-alpha.

Chronic infection with hepatitis C virus is an insidious and slow-progressing disease having a significant impact on the quality of life. It can eventually result in cirrhosis of the liver, decompensated liver disease and/or hepatocellular carcinoma.

Combination treatment with interferon alfa-2b and ribavirin of patients with chronic hepatitis C is disclosed by Reichard et al. (The Lancet 1998; 351:83-87; and T. Poynard et al. (The Lancet, 1998, Vol. 352, Oct. 31, p 1426-1432). See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492); and G. L. Davis et al. (N. Engl. J. Med., 1998, 339:1493-1499). However, this combination therapy is not always effective due to side effects associated ribavirin such as ribavirin-related hemolysis, and anemia.

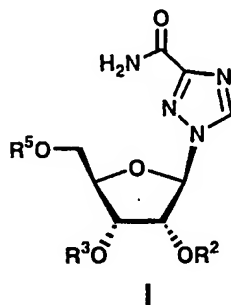


There is a definite need for more potent, safer ribavirin derivatives having fewer side effects for use as monotherapy or in combination with antiviral agents, e.g., interferon-alpha, to treat patients having susceptible viral infections, e.g., chronic hepatitis C infections, in a long-term, effective manner.

5

### SUMMARY OF THE INVENTION

The present invention provides a compound represented by formula I



10

wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^2$ ,  $R^3$  or  $R^5$  is  
 15 H,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}$ ,  $(HO)_2PO-$ ,  
 $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$  and wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is not H;  
 wherein  $R^6$  is H, alkyl, alkanoyl, aryl, heterocyclic, cycloalkyl,  $NR^{7a}R^{7b}$ , alkenyl, or  
 alkynyl;  
 or  $R^6$  is alkyl, alkanoyl, alkenyl or alkynyl substituted by halo, phenyl, cycloalkyl,  
 20  $NR^{7a}R^{7b}$ , hydroxy, or alkoxy;

or  $R^6$  is aryl substituted by phenyl; halo, CN,  $NO_2$ , OH,  $R^{18}$ ,  $CF_3$ , SH,  
 $SR^{7a}$ ,  $SOR^{7a}$ ,  $SO_2R^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $CO_2H$ ,  $CO_2^-$ ,  $OR^{7a}$ ,  $O^-M^+$  or  $S^-M^+$   
 wherein  $M^+$  is an alkali metal,

25

W is O,  $NR^{18}$  or S;



$R^{7a}$  is H, alkyl, alkanoyl, or aryl; or  $R^{7a}$  is alkyl, alkanoyl or aryl substituted by phenyl halo, CN, NO<sub>2</sub>, OH, CO<sub>2</sub>H, or alkoxy;  
and  $R^{7b}$  is H, alkyl or aryl or  $R^{7b}$  is alkyl or aryl substituted by phenyl halo, CN, NO<sub>2</sub>, OH, CO<sub>2</sub>H, or alkoxy;

5

or  $R^{7a}$  and  $R^{7b}$  taken together with N and one of CHR<sup>7a</sup>, NR<sup>7a</sup>, O, S, SO or SO<sub>2</sub> form a five-, six- or seven- membered ring;

$R^{17}$  is H, OR<sup>7a</sup>, NR<sup>7a</sup>R<sup>7b</sup>,  $R^6$ -(W)<sub>x</sub>-CO-,  $R^6$ -(W)<sub>x</sub>-CS-,  $R^6$ -(W)<sub>x</sub>-C=NR<sup>18</sup>-, (HO)<sub>2</sub>PO-,  $R^6$ -(W)<sub>x</sub>-PO(OH)- or HO-SO<sub>2</sub>-;

10

$R^{18}$  is H, alkanoyl or alkyl;  
and x = 0 or 1;

or a pharmaceutically acceptable salt thereof.

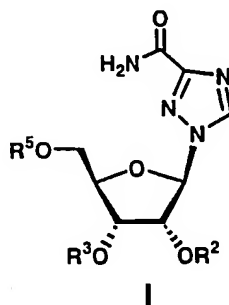
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The present invention provides a method of treating patients having a susceptible viral infection, such as a chronic hepatitis C infection

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The present invention provides a method of treating patients having comprising administering a therapeutically effective amount of a ribavirin derivative of formula I and a therapeutically effective amount of interferon-alpha for a time period sufficient to eradicate detectable HCV-RNA at the end of said period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin derivative is represented by formula I:

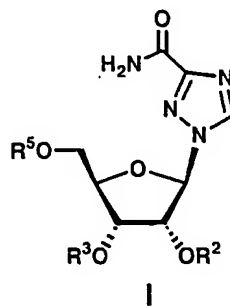
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The present invention also provides a method of treating patients having chronic hepatitis C infection comprising administering a therapeutically effective amount of a

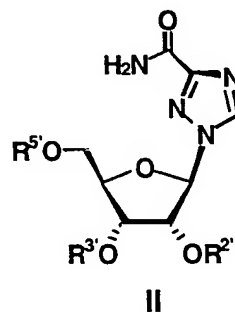


ribavirin derivative of formula I and a therapeutically effective amount of interferon-alpha for a time period of at least 20 to 50 weeks to eradicate detectable HCV-RNA at the end of said 20 to 50 week period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin derivative is represented by the formula I:



10

The present invention provides a compound represented by formula II



wherein at least one of R²', R³' or R⁵' is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of R²', R³' or R⁵' is a natural or unnatural α-amino acid residue.

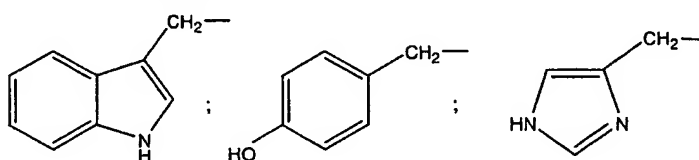
In a preferred embodiment, the natural or unnatural α-amino acid residues for the compounds of formula II are represented by the formulas

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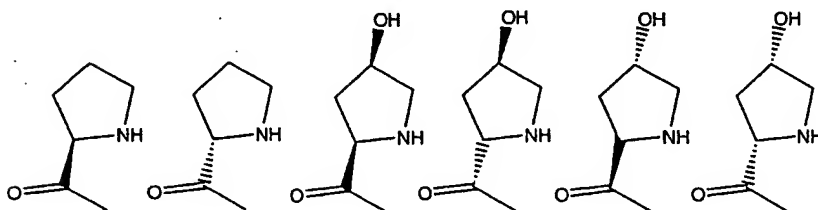


Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



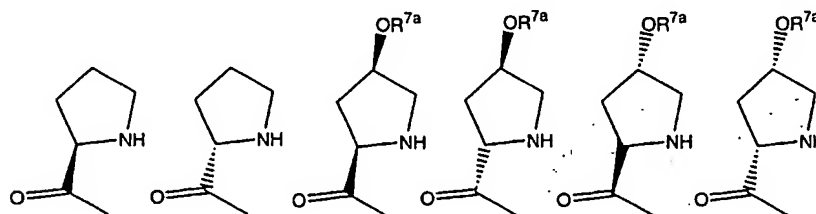
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof;

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof;

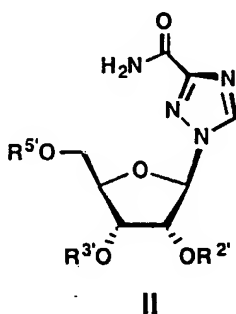
or Y taken together with the  $\alpha$  carbon and N form



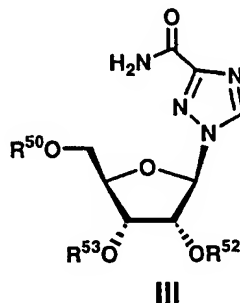
or a pharmaceutically acceptable salt thereof;



In another embodiment, the present invention relates to a method of treating patients having chronic hepatitis C infection comprising administering a therapeutically effective amount of a ribavirin derivative of formula II and a therapeutically effective amount of interferon-alpha for a time period sufficient to eradicate detectable HCV-RNA at the end of said period of administering and to have no detectable HCV-RNA for at least 24 weeks after the end of said period of administering, and wherein the ribavirin derivative is represented by formula II



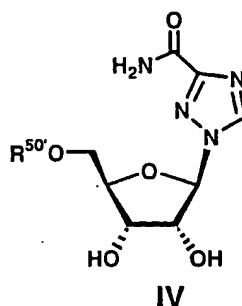
The present invention also provides a compound represented by formula III



wherein at least one of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  is a straight or branched chain polyalkylene oxide polymer conjugate, and the remaining two of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  are independently H or a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof. In a preferred embodiment,  $R^{52}$  and  $R^{53}$  in the compounds of Formula III are each H.



The present invention further provides a compound represented by the formula IV



5        wherein R<sup>50'</sup> is a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof.

10        The present invention also provides pharmaceutical compositions for treating susceptible viral infections comprising a compound of formula IV and at least one pharmaceutically acceptable carrier.

15        The present invention also provides a method of treating a patient with a susceptible viral infection which comprises administering to said patient an effective amount of a compound of formula IV

20        The present invention also provides a method of treating a patient infected with chronic hepatitis C which comprises administering to said patient an effective amount of a compound of formula IV in association with an effective amount of an interferon alfa for a time sufficient to eradicate detectable HCV-RNA levels.

#### DETAILED DESCRIPTION

25        The term "alkyl" as used herein means straight and branched carbon chains of one to twenty carbons, preferably one to six carbons, and more preferably one to three carbons.



The term "alkenyl" as used herein means straight and branched chain alkyl groups containing at least one carbon-carbon double bond and two to twenty carbons, preferably two to eight carbons.

5       The term "alkynyl" as used herein means straight and branched chain alkyl groups containing at least one carbon-carbon triple bond and two to twenty carbons, and preferably two to six carbons containing at least one carbon-carbon triple bond.

10       The term "cycloalkyl" as used herein means carbocyclic rings of three to twelve carbons, preferably three to seven carbons, and more preferably three to six carbons optionally substituted by one double bond.

15       The term "alkanoyl" as used herein means straight and branched chain alkanoyl groups of one to twenty carbons, preferably two to twelve, more preferably two to ten and most preferably two to six carbons.

20       The term "alkenoyl" as used herein means straight and branched chain alkenoyl groups of one to twenty carbons containing at least one carbon-carbon double bond, preferably two to twelve, or more preferably two to ten and most preferably two to six carbons containing at least one carbon-carbon double bond.

The term "halo" as used herein means fluorine, chlorine or bromine, preferably fluorine or chlorine.

25       The term "alkynoyl" as used herein means straight and branched chain alkynoyl groups of one to twenty carbons containing at least one carbon-carbon triple bond, preferably two to twelve, or more preferably two to ten and most preferably two to six carbons containing at least one carbon-carbon triple bond.

30       The term "alkoxy" as used herein means straight and branched chain alkyl groups containing one bond to oxygen at the one carbon and one to ten carbons. Typically suitable alkoxy includes methoxy, ethoxy and tert-butoxy.

35       The term "aryl" as used herein (including the aryl portion of aryloxy and aralkyl, e.g., benzyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), or is a polycyclic aromatic containing one or more heteroatoms, e.g., N or S such as quinoyl, isoquinoyl with all

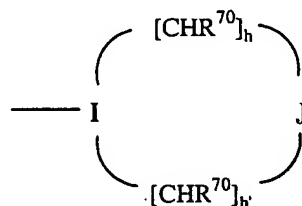


available substitutable carbon atoms of the carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halogen, alkyl, hydroxy, alkoxy, CN, phenoxy, CF<sub>3</sub>, amino, alkylamino, dialkylamino, SH, S<sup>-</sup> M<sup>+</sup> or -NO<sub>2</sub>; and the term "M<sup>+</sup>" represents an alkali metal cation such as Na<sup>+</sup>, K<sup>+</sup> and Li<sup>+</sup>.

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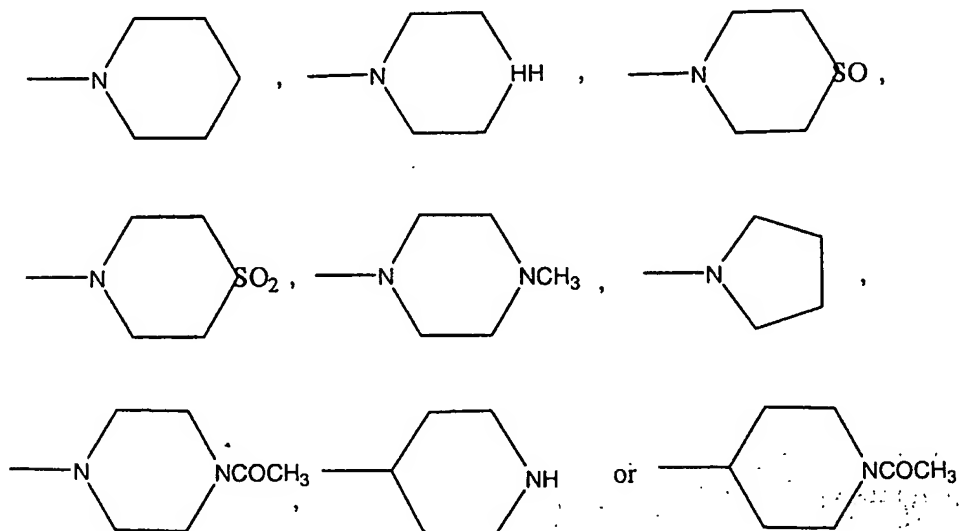
The term "arylalkyl" as used herein means an alkyl group substituted by an aryl group.

10 The term "heterocyclic" as used herein means a cyclic group represented by the formula;



wherein J is -CHR<sup>70</sup>-, -O-, -NR<sup>70</sup>-, -S-, -SO- or -SO<sub>2</sub>-, and I is -CR<sup>70</sup> or -N-; and R<sup>70</sup> is H, alkyl or aryl; and h and h' are independently 1 to 4 and the sum of h + h' is 2, 3, 4 or

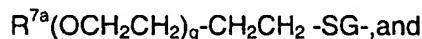
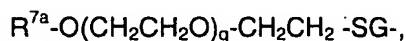
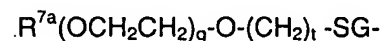
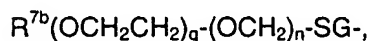
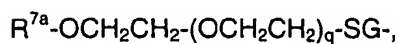
15 5. Typically suitable heterocyclics include





The term "halo" as used herein means fluoro, chloro, bromo or iodo, preferably fluoro or chloro.

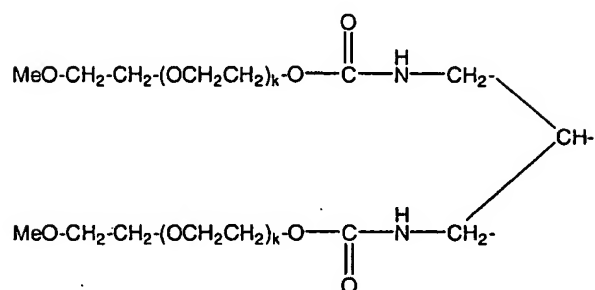
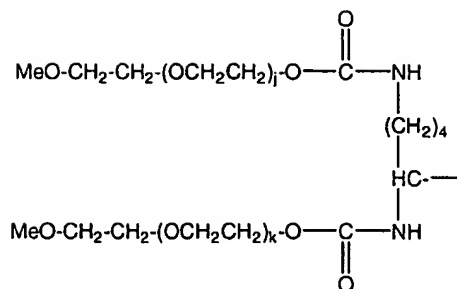
The term "straight or branched chain polyalkylene oxide polymer conjugate" as used herein means a (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide polymer having a terminal spacer group(SG). Typically suitable (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide polymers having a terminal spacer group(SG) include .



m = 0 to 100; n = 0 to 6000; t = 1 to 4; and q = 1 to 5000; and SG is as defined hereinbelow.

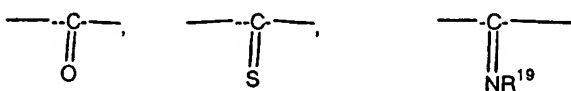
The (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyalkylene oxide conjugates include (C<sub>1</sub>-C<sub>3</sub>)alkoxy polyethylene oxide polymer conjugates, especially methoxy-CH<sub>2</sub>-CH<sub>2</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>j</sub>-SG and (C<sub>1</sub>-C<sub>3</sub>)alkoxy polypropylene oxide polymer conjugates, especially -(C<sub>1</sub>-C<sub>3</sub>)alkoxy C(CH<sub>3</sub>)H-CH<sub>2</sub>-(OC(CH<sub>3</sub>)HCH<sub>2</sub>)<sub>j</sub>-SG. Typically suitable branched-chain polyethylene oxide polymer conjugates include the following



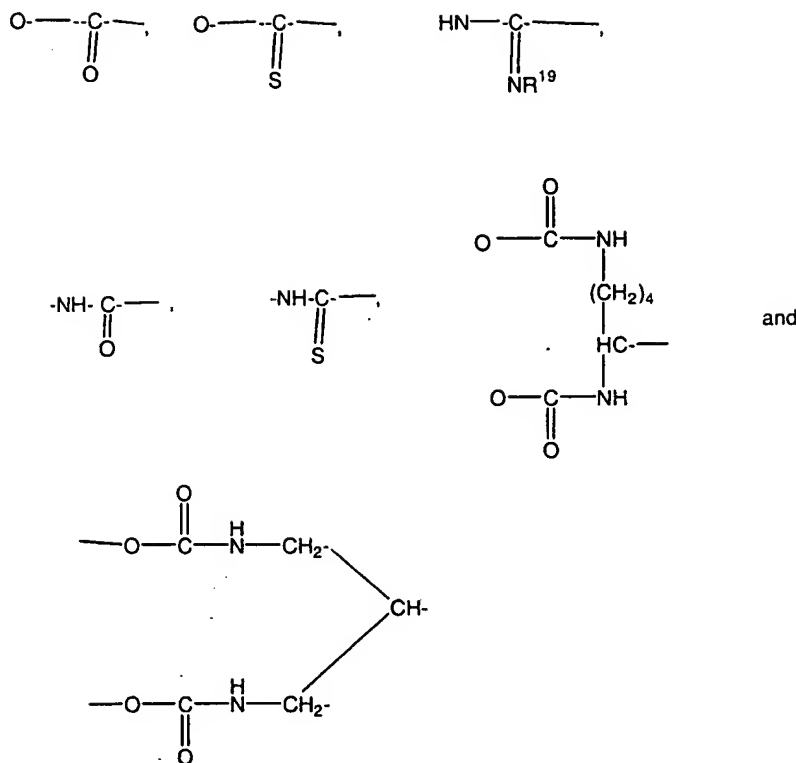


wherein j and k are independently 400 to 600, preferably each is 420 to 460.

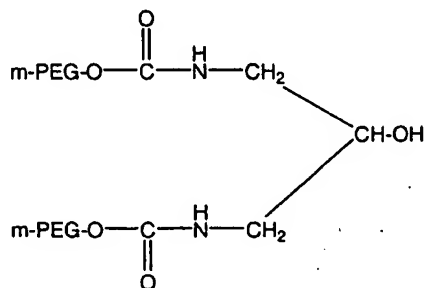
Typically suitable spacer groups (SG) include





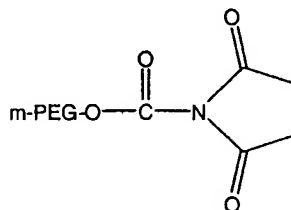


These branched chain polymer conjugates are disclosed in EP0 809 996 and are available from Shearwater Polymers Inc., Huntsville, Ala. Other branched chain polyalkylene oxide conjugates are the methoxy polyethylene glycol conjugates disclosed in U.S. Patent No.5,642,575. See especially the examples on col 9, line 38 to col.13, line 60. Methoxy polyethylene glycols (m-PEG-) are available from Union Carbide Corp., Danbury, Conn. Exemplary methoxy polyethylene glycol conjugates are disclosed in U.S. Patent No.5,642,575. Include

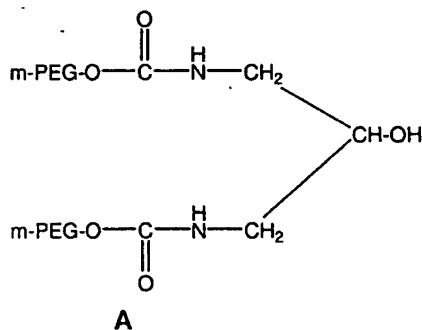




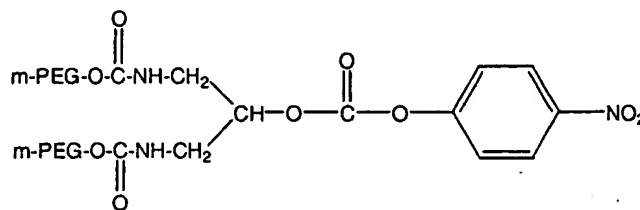
These branched chain polymer conjugates may be prepared in accordance with the procedures of U.S. Patent No 5,122,614: using for example methoxy-polyethylene glycol ("m-PEG") having a MW = 5000 to form methoxy-poly(ethylene glycol)-N-succinimidyl carbonate(SC-PEG);



In accordance with the procedures of U.S. Patent No.5,642,575., SC-PEG is reacted with 1,3-diamino-2-propanol in an aprotic solvent such as methylene chloride at room temperature to give the compound of the formula A

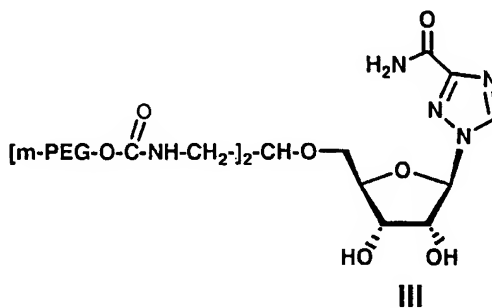


The compound of the formula A is treated with an activating group, e.g., p-nitrophenyl chloroformate under anhydrous conditions in the presence of a base such as pyridine to give the activated compound of formula B:

**B**

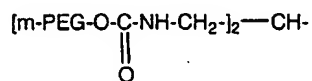


Reaction of the activated compound of formula B: with benzyldene ribavirin-  
compound 2 of Example 1 of this invention- provides the the branched chain  
methoxy-polyethylene glycol conjugate of ribavirin of formula III;



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wherein  $R^{50}$  is



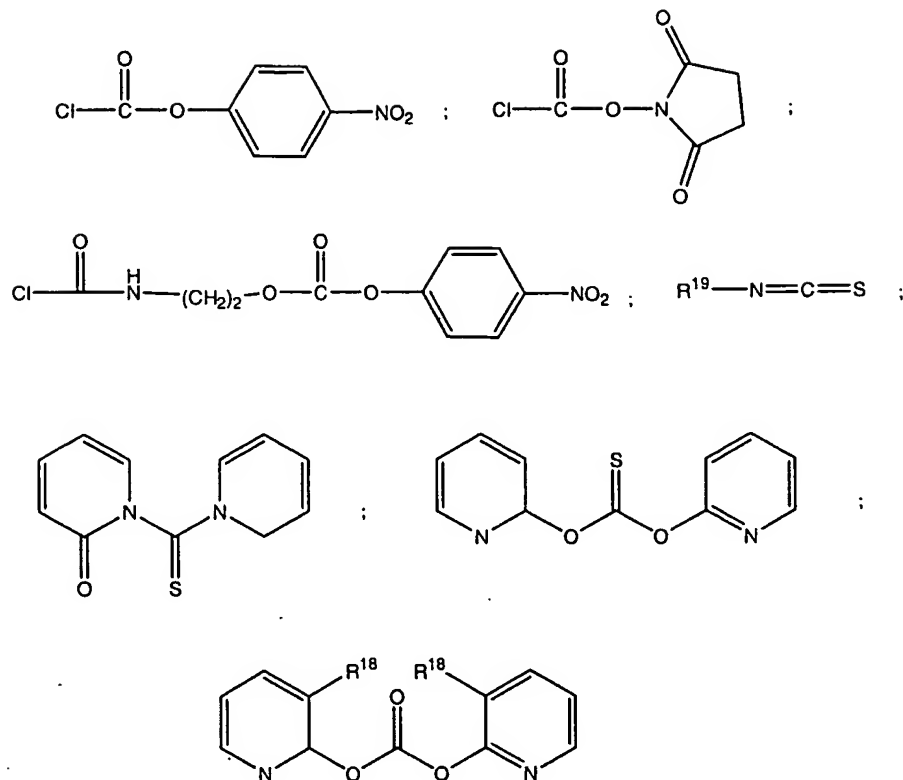
and wherein m-PEG is methoxy-polyethylene glycol.

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Typically suitable activating groups include

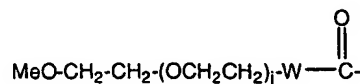


15



- wherein  $R^{19}$  is  $(C_1-C_8)$ alkyl or  $(C_3-C_8)$ cycloalkyl, and preferably  $R^{19}$  is methyl;  $R^{18}$  is H, alkanoyl or alkyl and preferably  $R^{18}$  is methyl. See European Patent applications
- 5 EP 0510356 and EP0236987 for the preparation of the above listed activating groups.

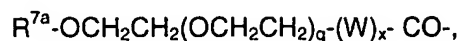
- Preferred straight chain polyalkylene oxide polymer conjugates include  $(C_1-C_3)$ alkoxy-polyalkylene oxide polymer especially methoxy-polyethylene glycol
- 10 conjugates such as wherein  $j$  is 400 to 800



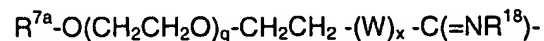
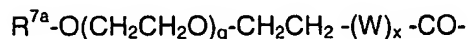
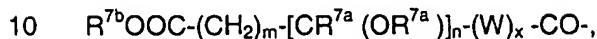
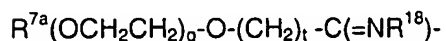
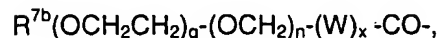
- 15 In preferred embodiments of the present invention, the compounds of formula I have at least one of  $R^2$ ,  $R^3$  and  $R^5$  equal to a straight chain polyalkylene oxide polymer



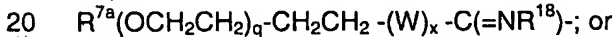
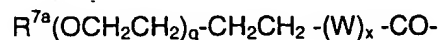
conjugate ; wherein the straight chain polyalkylene oxide polymer conjugate is selected from



5



15



$W = -O- \text{ or } -NR^{18}-; \text{ and } R^{18} = H;$

$m = 0 \text{ to } 100; n = 0 \text{ to } 6000; t = 1 \text{ to } 4; \text{ and } q = 1 \text{ to } 5000.$

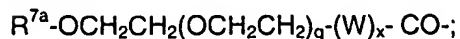
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In another preferred embodiment of the present invention, the compounds of formula I have  $R^2 = R^3 = H$  and  $R^5$  is one of the above listed straight chain polyalkylene oxide polymer conjugates.

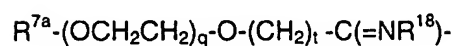
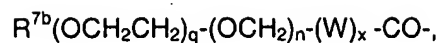
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In another preferred embodiments of the present invention, the compounds of formula II have at least one of  $R^2$ ,  $R^3$  and  $R^5$  equal to a straight chain polyalkylene oxide polymer conjugate; wherein the straight chain polyalkylene oxide polymer conjugate is selected from

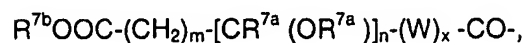
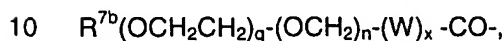
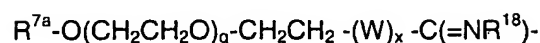
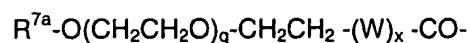
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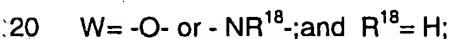
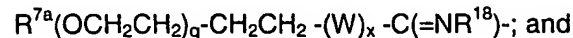
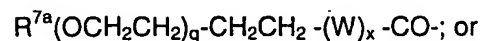




5



15



and

$m = 0 \text{ to } 100; n = 0 \text{ to } 6000; q = 1 \text{ to } 5000; t = 1 \text{ to } 4; \text{ and } x = 0 \text{ or } 1.$

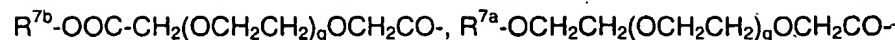
In another preferred embodiment of the present invention, the compounds of formula II

25 have  $R^{2'} = R^{3'} = H$  and  $R^{5'}$  is one of the above listed straight chain polyalkylene oxide polymer conjugates.

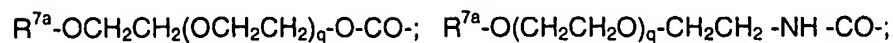
In more preferred embodiments of the present invention, (a) wherein the

30 compounds of formula I have  $R^2 = R^3 = H$  and (b) wherein the compounds of formula II have  $R^2 = R^3 = H$ ,  $R^5$  and  $R^{5'}$  are independently one of the following preferred straight chain polyalkylene oxide polymer conjugates:

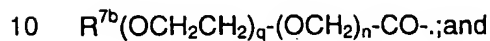
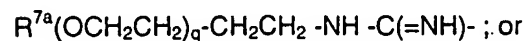
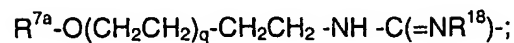
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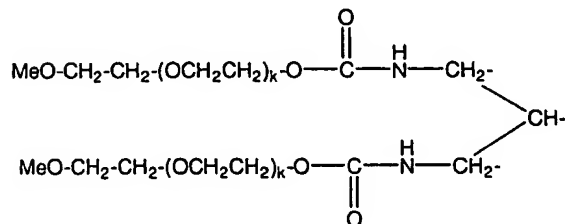
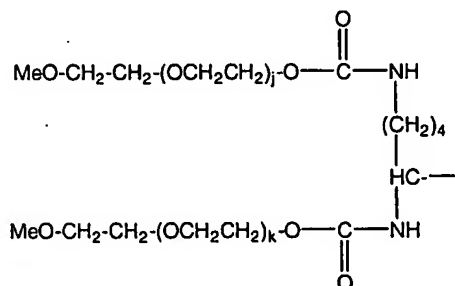
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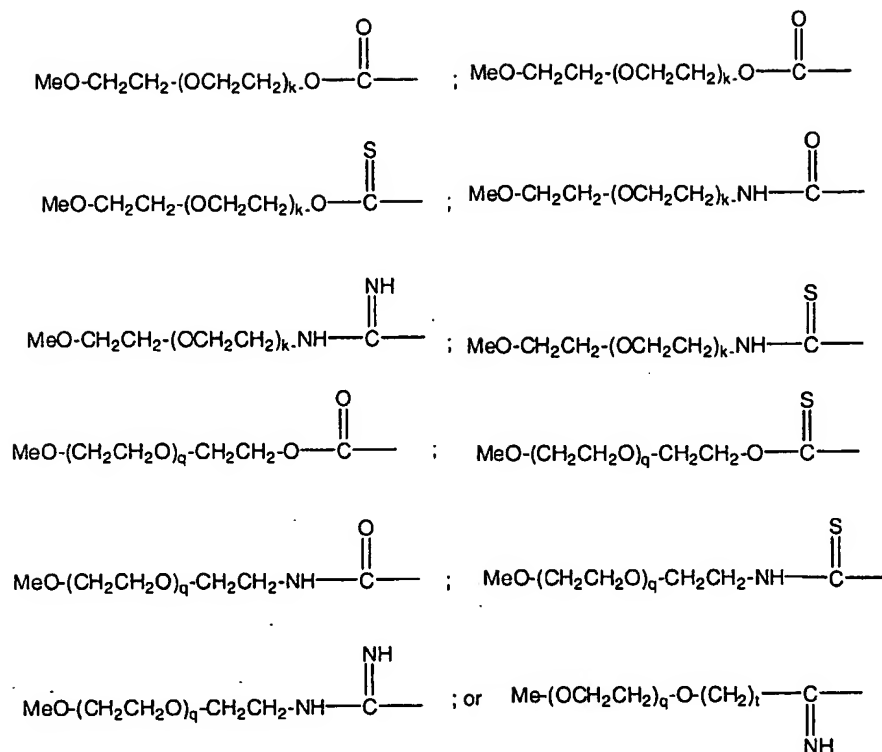
$n = 0$  to  $6000$ ; and  $q = 1$  to  $5000$ .

Exemplary methoxy-polyethylene glycol conjugates include

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The methoxy- polyethylene glycol conjugates can readily be prepared and their molecular weight determined by one skilled in the art view of known methods such as described in European Patent Applications EP0236987 and EP0510356. The starting polyethylene glycols (PEG) and PEG monomethyl ethers of various molecular weights e.g. 750, 1900, 5000, 10,000 can readily be prepared by methods known in the art or can be obtained from commercial sources.

- 10 In a preferred embodiment of the present invention, compounds of formula I have  $R^2=R^3=H$  and  $R^5$  equal to  $R^6(W)_x\text{CO-}$ ,  $(\text{HO})_2\text{P=O-}$  or  $R^6(W)_x\text{PO(OH)-}$ . In the preferred embodiments of  $R^6\text{-(W)}_x\text{CO-}$  and  $R^6(W)_x\text{-PO(OH)-}$ ,  $W=\text{O}$  or  $\text{NH}$  and  $x=0$  or  $1$ . In other preferred embodiments of  $R^6\text{-(W)}_x\text{CO-}$  and  $R^6(W)_x\text{P(OH)O-}$  include  $R^{17}(\text{CH}_2)_m\text{-NR}^{7b}R^{7a}\text{-(CH}_2)_n\text{OCO-}$  and  $R^{17}(\text{CH}_2)_m\text{-NR}^{7b}R^{7a}\text{-(CH}_2)_n\text{-O-PO(OH)}$ , wherein  $m=0$  to  $4$  and  $n=0$  to  $4$ ; and  $R^{17}$  is  $\text{H}$ ,  $\text{Me}$ ,  $\text{MeCO-}$  or  $\text{Me}_2\text{N-}$ , and  $R^{7a}$   $R^{7b}\text{N(CH}_2)_f\text{-(CHR}^{7a}\text{)}_e\text{OCO-}$  or  $R^{7a}R^{7b}\text{N(CH}_2)_f\text{-(CHR}^{7a}\text{)}_e\text{CO-}$ ; wherein  $f=0$  to  $4$  and  $e=1$  to  $5$ , and  $R^{7a}R^{7b}\text{N}$  is  $\text{Me}_2\text{N-}$ ,  $\text{MeHN-}$  or  $\text{MeCONH-}$ .
- 15

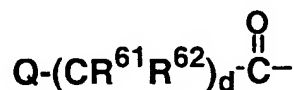


In most preferred embodiments of the compounds of formula I,  $x$  in  $R^6(W)_xCO-$ , is equal to 0.

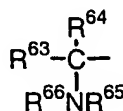
5 In another preferred embodiment of the compounds of formula I, one of  $R^2$ ,  $R^3$  or  $R^5$  is  $R^6CO$  and  $R^6CO$  is a natural or unnatural  $\alpha$ -amino acid residue.

In another preferred embodiment of the compounds of formula II, one of  $R^2$ ,  $R^3$  or  $R^5$  is a natural or unnatural  $\alpha$ -amino acid residue.

10 The term "a natural or unnatural  $\alpha$ -amino acid residue" as used herein means a residue represented by the formula



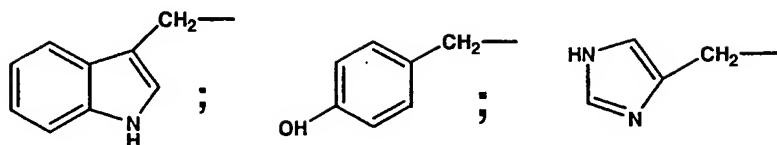
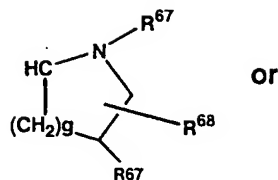
15 wherein Q is



wherein  $R^{61}$  and  $R^{62}$  are independently H, alkyl, alkenyl, alkynyl,  $(C_3-C_7)$ cycloalkyl, arylalkyl, or alkyl, alkenyl, alkynyl,  
 20  $(C_3-C_7)$ cycloalkyl, arylalkyl, substituted by halo, OH, SH,  $CF_3$ ,  $SR^{67}$ ,  $OR^{67}$  or  $NR^{65}R^{66}$  or wherein  $R^{61}$  and  $R^{62}$  taken together with the carbon atom in  $(CR^{61}R^{62})$  form a cyclopropane, cyclobutane, cyclopentane, or cyclohexane.;

wherein  $R^{63}$  and  $R^{64}$  are independently H, alkanoyl, alkyl, aryl, arylalkyl, alkenyl, alkynyl,  
 25 or alkanoyl, alkyl, aryl, arylalkyl, alkenyl, alkynyl substituted by halo, OH, SH,  $CF_3$ ,  $SR^{67}$ ,  $OR^{67}$ ; or  $R^{63}$  and  $R^{64}$  are independently





wherein  $R^{67}$  is H, alkyl, alkanoyl, alkenoyl, aryl, arylalkyl, alkenyl, alkynyl, or, alkyl, aryl, arylalkyl, alkenyl, alkynyl substituted by halo, OH, SH,  $CF_3$ , alkanoylthienyl, or alkanoyloxy;

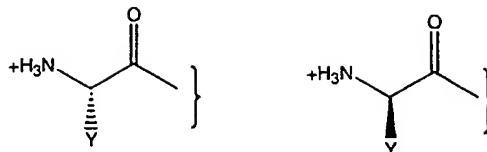
wherein  $R^{68}$  is H, alkyl, aryl, arylalkyl, alkenyl, or alkynyl;

and g is 0, 1 or 2; d is 1 or 2;

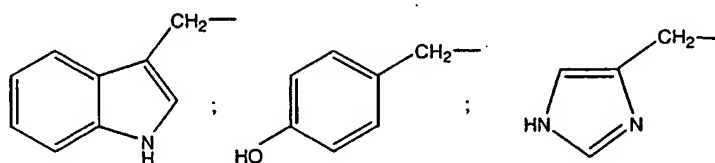
In a more preferred embodiments of the compounds of formulas I and II, the preferred natural or unnatural  $\alpha$ -amino acid residues are selected from-



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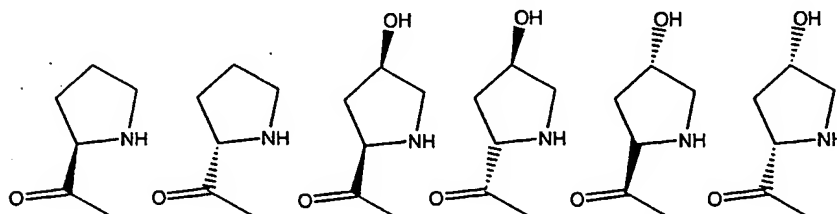


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof;

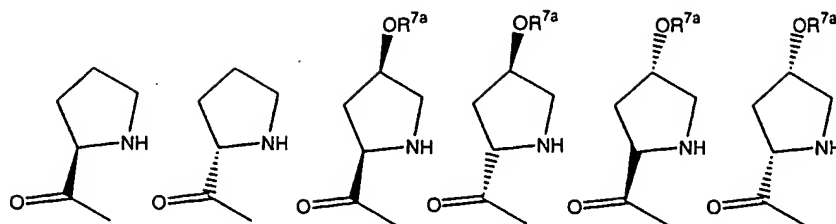
or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.

or



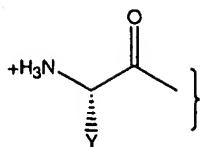


wherein R<sup>7a</sup> is as defined hereinabove; or a pharmaceutically acceptable salt thereof.

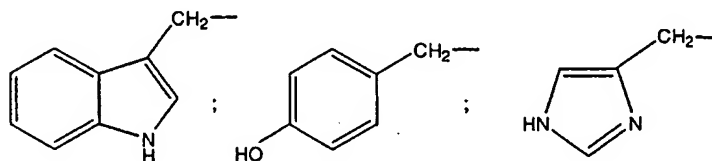
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In another more preferred embodiment of the compounds of formulas I and II, the preferred natural  $\alpha$ -amino acid residues are selected from



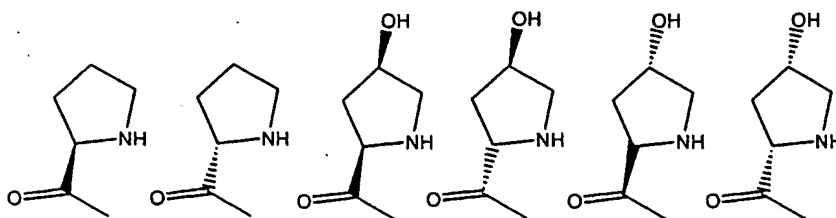


Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



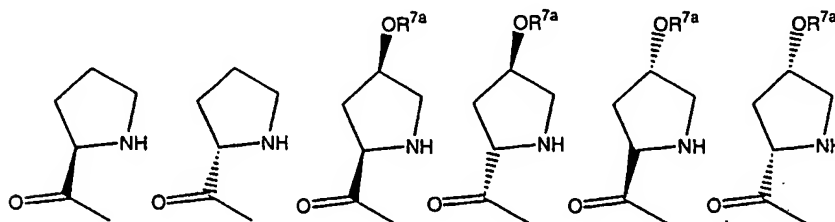
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)-; or a pharmaceutically acceptable salt thereof

or Y taken together with the  $\alpha$  carbon and N form



or

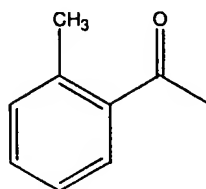
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wherein R<sup>7a</sup> is as defined hereinabove;  
or a pharmaceutically acceptable salt thereof.



Other preferred embodiments for R<sup>6</sup>CO in the compounds of formula I include



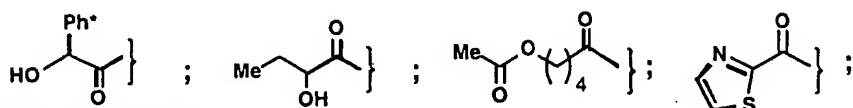
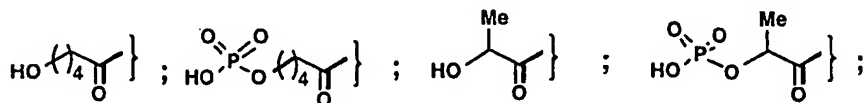
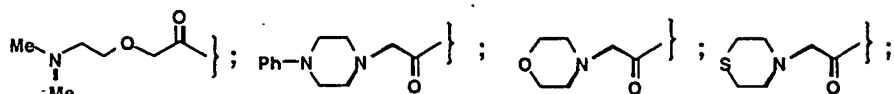
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(CH<sub>3</sub>)<sub>3</sub>CO-, C<sub>6</sub>H<sub>5</sub>CO-, (HO)<sub>2</sub>PO - and

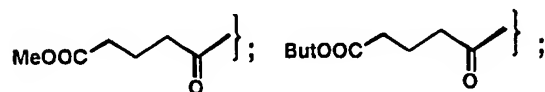
L-C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OCONHCH(CH<sub>3</sub>)CO-, i.e., C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OCONHCH

10

or R<sup>6</sup>CO is



\*(and substituted Ph)



15

or a pharmaceutically acceptable salt thereof;

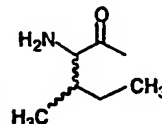
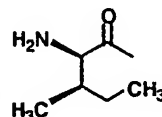
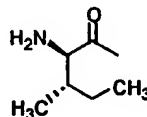
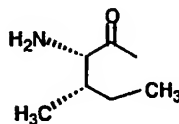
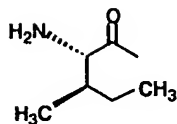
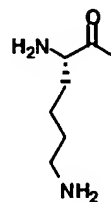
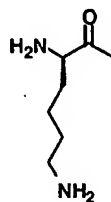
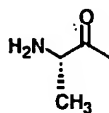
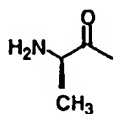
wherein Ph is phenyl and phenyl substituted by halo, CN, NO<sub>2</sub>, OH, CO<sub>2</sub>H, or alkoxy.



The most preferred natural or unnatural amino acid residues in the compounds of formulas I and II are represented by the formulas in Table AA herein below:

**TABLE AA**

5



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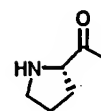
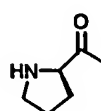
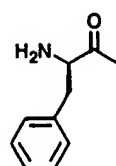
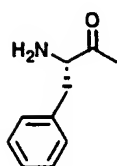
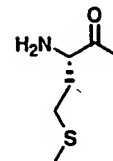
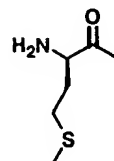
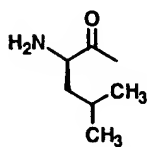
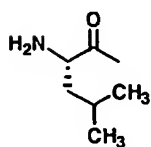
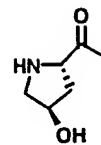
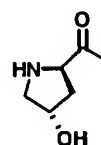
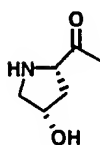
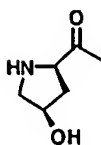
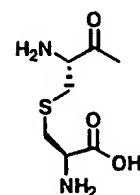
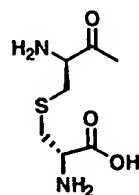
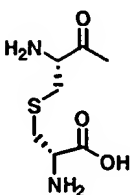
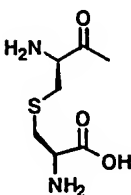
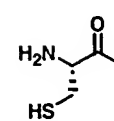
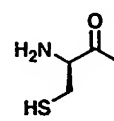
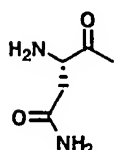
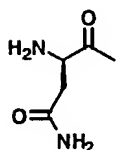
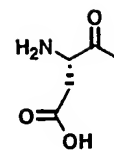
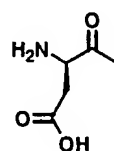
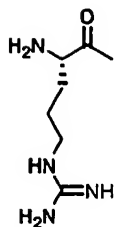
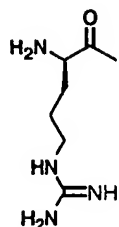
TABLE AA cont.



TABLE AA cont.

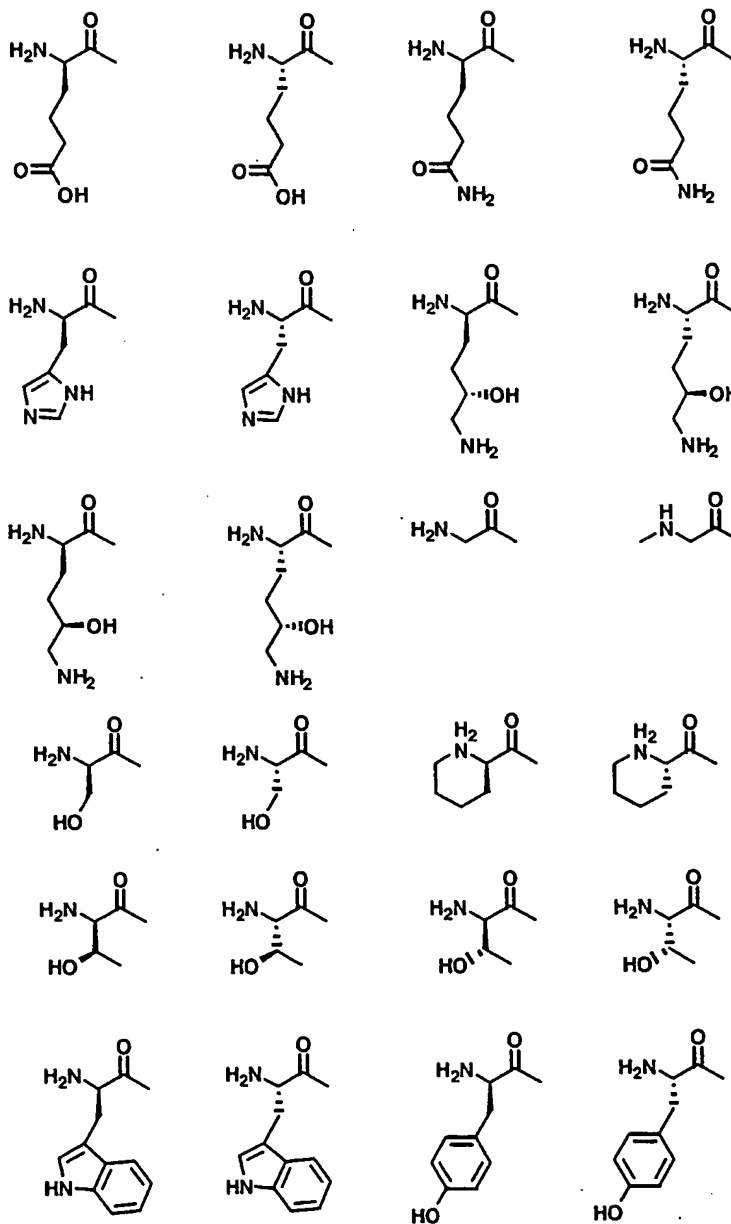
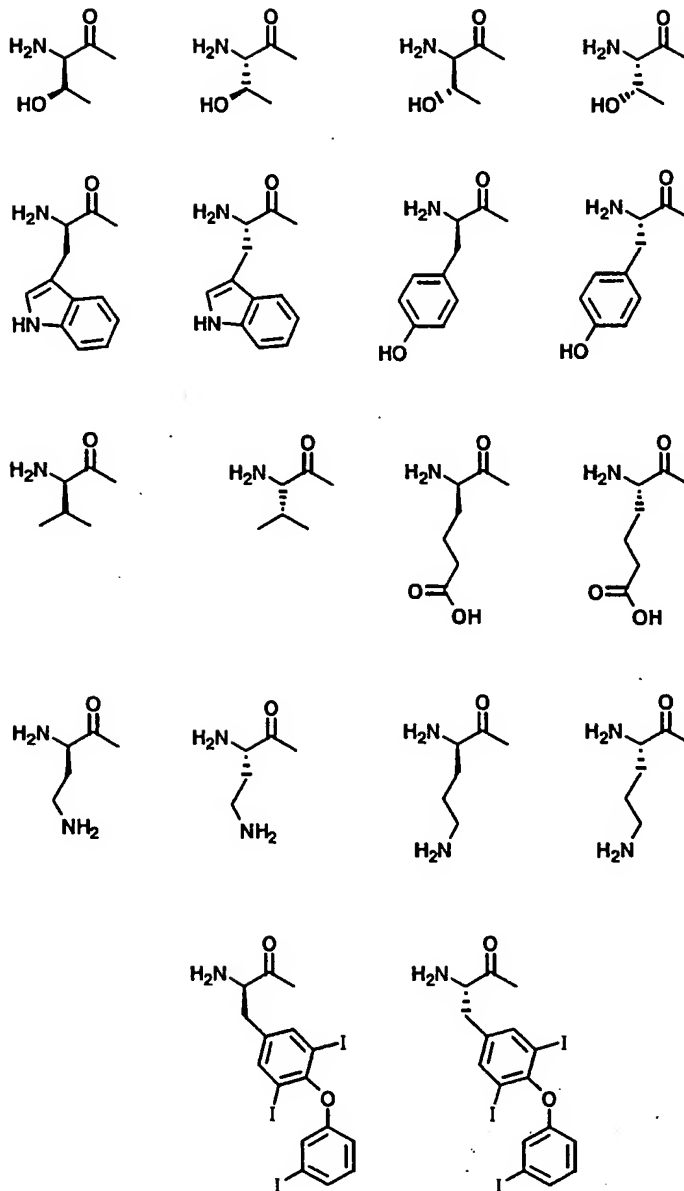




TABLE AA cont.





The compounds of formulas I to IV metabolize *in vivo* into ribavirin and are useful for treating susceptible viral infections treatable with ribavirin, alone, or in combination with other ant-viral therapies .eg., interferon-alfa, and so- called Highly Active Antiretroviral Therapy ("HAART"). A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART") ; HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse trans-cryptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). The treating of patients having chronic hepatitis C with the compounds of formulas I-VIII is performed as part of a combination therapy with interferon-alfa, including interferon alfa-2a, interferon alfa-2b, consensus interferon especially interferon alfa-2b as well as pegylatyed interferon alfa-2a and pegylatyed interferon alfa-2b.

The present invention provides methods and pharmaceutical compositions containing a compound of formulas I-IV for treating susceptible viral infections , especially hepatitis C viral infections.

The term "susceptible viral infections" as used herein means viral infections caused by a wide range of RNA and DNA viruses, including, but not limited to, the families of viruses such as flaviruses-including the genus flavivirus, pestivirus of which Kunjin virus is a member, and heparivirus of which hepatitis C virus is a member, and arbovirus of which the West Nile virus is a member- orthomyxoviruses, paramyxoviruses, arenaviruses, bunyaviruses, herpes viruses, adenoviruses, poxviruses, and retroviruses.

Typical suitable "susceptible viral infections" include influenza A and B viral infections; parainfluenza viral infections, respiratory syncytial virus("RSV") infections such as RSV bronchiolitis and RSV pneumonia especially such RSV infections in children and infants as well as RSV pneumonia in patients with preexisting cardiopulmonary disease, measles viral infections, Lassa fever viral infections, Korean Haemorrhagic fever infections, hepatitis B viral (HBV) infections, Crimean-Congo-Haemorrhagic and HCV infections and HIV-1 infections, encephalitis infections such as caused by West Nile virus or Kunjin virus or the St. Louis encephalitis infections as well.



as viral infections found in immunocompromised patients. Other susceptible viral infections are disclosed in USP 4,211,771 at column 2, line 21 to column 3 line 37; doses and dose regimens and formulations are disclosed at column 3, line 4 to column 9, line 5; see also Canadian Patent No. 1,261, 265. Sidwell, R.W., et al. Pharmacol. Ther., 1979, Vol 6 pp 123-146 discloses that the in vivo antiviral experiments conducted with ribavirin generally confirm one broad-spectrum antiviral activity seen in vitro and states that the efficacy of ribavirin is quite dependent upon the site of infection; the manner of treatment; the age of the animal and the virus dosage utilized. Tables 4 and 5 on page 127 list the RNA and DNA virus infections significantly inhibited in vivo by ribavirin.

The *in vitro* inhibitory concentrations of ribavirin are disclosed in Goodman & Gilman's "The Pharmacological Basis of Therapeutics", Ninth Edition, (1996) McGraw Hill, NY, at pages 1214-1215. The Virazole product information discloses a dose of 20 mg/mL of Virazole aerosol for 18 hours exposure in the 1999 Physicians Desk Reference at pages 1382 - 1384.

Ribavirin dosage and dosage regimens are also disclosed by Sidwell, R.W., et al. Pharmacol. Ther 1979 Vol 6. pp123-146 in section 2.2 pp 126-130. Fernandes, H., et al., Eur. J. Epidemiol., 1986, Vol 2(1) pp1-14 at pages 4-9 disclose dosage and dosage regimens for oral, parenteral and aerosol administration of ribavirin in various preclinical and clinical studies.

The term "patients having hepatitis C infections" as used herein means any patient-including a pediatric patient- having hepatitis C and includes treatment-naïve patients having hepatitis C infections and treatment-experienced patients having hepatitis C infections as well as those pediatric, treatment-naïve and treatment-experienced patients having chronic hepatitis C infections.

These patients having hepatitis C include those who are infected with multiple HCV genotypes including type 1 as well as those infected with, e.g., HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.



The term "treatment-naive patients having hepatitis C infections" as used herein means patients with hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

5           The term "treatment-experienced patients having hepatitis C infections" as used herein means patients with hepatitis C who have been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa, including relapsers and non-responder.

10           The term "relapsers" as used herein means treatment-experienced patients with hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

15           The term "non-responders" as used herein means treatment-experienced patients with hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

20           When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), preferably in the range of about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once  
25 a week (QW) or in the range of about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW), or is in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about  
30 0.25 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, or is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, most preferably is in the range of



about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 0.75 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week.

5           When the pegylated interferon-alfa administered to pediatric patients is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice  
10 a week(BIW), more preferably about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), or about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week(BIW), more preferably about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b  
15 administered once a week, or preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered in single or divided doses, preferably once a week (QW) or twice a week(BIW), more preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b  
20 administered twice a week, and most preferably about 2.25 to about 2.6 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 1.1 to about 1.3 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week(BIW).

25           When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in accordance with the present invention, is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 150 micrograms to about 250  
30 micrograms QW or the effective amount is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 100 micrograms to about 125 micrograms twice a week.



When the pegylated interferon-alfa administered to a pediatric patient is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in accordance with the present invention, is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 300  
5 micrograms to about 375 micrograms QW or the therapeutically effective amount of pegylated interferon alfa-2a administered to a pediatric patient is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 150 micrograms to about 190 micrograms once a week

10 The esters of ribavirin represented by formulas I-IV are administered to the patient having chronic HCV in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of esters of ribavirin represented by formulas I-IV. The  
15 amount of esters of ribavirin represented by formulas I-IV administered concurrently with the pegylated interferon-alfa is from about 200 to about 1600 mg per day, preferably about 300 to about 1200 mg/day or about 400 to about 800 mg day and most preferably about 400 to about 600 mg a day. The pegylated interferon-alfa dose is also preferably administered to the pediatric patient during the same period of time that such patient  
20 receives doses of the esters of ribavirin represented by formulas I-IV. The amount of the 5'-amino acid esters of ribavirin represented by formulas I-IV administered to the pediatric patient having chronic HCV concurrently with the interferon-alfa is from about 1 to about 30 mg per kilogram per day, preferably from about 4 to about 15 mg per kilogram per day, more preferably about 6, 8 or 15 mg per kilogram per day, most  
25 preferably about 8 to 10 mg per kilogram per day in divided doses.

Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by sub-cutaneous(SC), intravenous(IV), or intramuscular(IM) injection. The  
30 compounds represented by formulas I-IV may be administered orally in capsule, tablet, or liquid form, intranasally as an aerosol by nasal spray or parenterally, preferably by SC, IV, or IM injection. The esters of ribavirin represented by formulas I-IV may be orally



administered in association with the parenteral administration of pegylated interferon-alfa . Of course, other types of administration of both medicaments, as they become available, are contemplated, such as transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long  
5 as the proper dosages are delivered without destroying the active ingredient

The term " interferon-alfa " as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b, such as Intron-A interferon available from Schering  
10 Corporation, Kenilworth, N.J., recombinant interferon alfa-2a, such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2c, such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons, such as  
15 Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon, such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made  
20 by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

25

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG<sub>12000</sub>-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alfa"  
30 and "PEG<sub>12000</sub>-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane.



linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG<sub>12000</sub>-interferon alfa-2b is prepared by attaching a PEG polymer  
5 to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG<sub>12000</sub> molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG<sub>12000</sub> attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery  
10 of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

Other pegylated interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include  
15 other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer  
20 conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

25 Pharmaceutical composition of pegylated interferon alfa suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients, e.g., sucrose, carriers, e.g., human or recombinant plasma albumin, tonicity agents, e.g. NaCl, preservatives, e.g., thimerosal,  
30 cresol or benyl alcohol, and surfactants, e.g., tweens or polysorbates in sterile water for injection. The pegylated interferon alfa may be stored as lyophilized powders under refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored



between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos. 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

10 A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

15 (a) elevated ALT,

(b) positive test for anti-HCV antibodies,

(c) presence of HCV as demonstrated by a positive test for the presence of HCV-RNA in the serum,

20 (d) clinical stigmata of chronic liver disease,

(e) hepatocellular damage.

25 The combination therapy of pegylated interferon-alfa and the esters of ribavirin represented by formulas I-IV may also be administered in association with anti-retroviral therapy, e.g., HAART, to the patient co-infected with the HIV-1 and HCV infection and exhibiting one or more of the above signs or symptoms in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms of the HCV infection, and to lower the HIV-1-RNA and HCV-RNA serum levels each by at least a power of ten, and preferably to eradicate detectable HCV-RNA at least by the end of about 20 to about 50 weeks, preferably at least 24 weeks to 48 weeks and to maintain no detectable HCV-

30



RNA for at least 24 weeks after the end of the about 20 to about 50 weeks.

Administration of the compounds represented by formulas I - IV may be discontinued after the end of the second time period depending upon the judgment of the attending clinician.

5

The term "no detectable HCV-RNA" in the context of the present invention means that there are fewer than 100 copies of HCV-RNA per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is 100 copies/mL. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

15

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

20 Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

25 Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

30



Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular compound and particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/kg/day to about 100 mg/kg/day, in two to four divided doses.



In a preferred embodiment of the present invention, those patients co-infected with HIV-1 and HCV infections are treated with pegylated interferon alfa in combination with the preferred 5'-amino acid esters of ribavirin represented by formulas III to VIII and a HAART combination considered appropriate by the attending clinician and the patient..

5 See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 1998, 339:1493-1499).

The preferred compounds of formulas I-IV are useful for treating patients having susceptible viral infections, e.g., chronic hepatitis C. The compounds of formulas III-VIII metabolize *in vivo* into ribavirin and are useful for treating susceptible viral infections treatable with ribavirin, alone, or in combination with other anti-viral therapies, e.g., interferon-alfa and HAART. The treating of patients having chronic hepatitis C with the compounds of formulas I-IV is performed as part of a combination therapy with interferon-alfa, especially interferon alfa-2b.

15 Compounds of formulas I-IV metabolize *in vivo* into ribavirin and produce higher plasma concentrations of ribavirin after oral administration of a compound of formulas I-IV to animals compared to administration of ribavirin.

20

The pharmaceutical compositions of the esters of ribavirin of the present invention (represented by formulas III & IV) may be adapted for any mode of administration e.g., for oral, parenteral, e.g., subcutaneous ("SC"), intramuscular ("IM"), intravenous ("IV") and intraperitoneal ("IP"), topical or vaginal administration or by inhalation (orally or intranasally). Preferably the ribavirin compounds represented by formula I are administered orally.

25 Such compositions may be formulated by combining a compound of formulas I-IV or an equivalent amount of a pharmaceutically acceptable salt of compound I with an suitable, inert, pharmaceutically acceptable carrier or diluent which may be either solid or liquid. The compounds of formulas I-IV are preferably converted into the pharmaceutically acceptable acid addition salts by adding to compounds of formulas I-

30



IV an equivalent amount (or two equivalents in the case of for example the lysine ester) of a pharmaceutically acceptable acid. Typically suitable pharmaceutically acceptable acids include the mineral acids, e.g.,  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$ ,  $\text{HCl}$ ,  $\text{HBr}$ , organic acids, including, but not limited to, acetic, trifluoroacetic, propionic, lactic, maleic, succinic, tartaric, glucuronic and citric acids as well as alkyl or arylsulfonic acids, such as p-toluenesulfonic acid, 2-naphthalenesulfonic acid, or methanesulfonic acid.

Typically suitable pharmaceutically acceptable salts include the following anions: acetate, adipate, besylate (benzenesulfonate), bromide, camsylate[(+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate], chloride, citrate, edisylate(1,2-ethanedisulfonate), estolate(dodecyl sulfate), fumarate, gluceptate(glucoheptonate), gluconate, glucuronate, hippurate, hyclate(hydrochloride, hemiethanolate), hydrobromide, hydrochloride, iodide, isethionate (2-hydroxyethanesulfonate), lactate, lactobionate, maleate, mesylate (methanesulfonate), methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate [4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate]], phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate(p-toluenesulfonate), triethiodide.;

and the following cations: benzathine (N,N-bis(phenylmethyl)-1,2-ethanediamine), calcium, diolamine (2,2-iminobis(ethanol), meglumine[1-deoxy-1-(methylamino)-D-glucitol], olamine(2-aminoethanol), potassium, procaine, sodium tromethamine [2-amino-2-(hydroxymethyl)-1,3 propanediol,] and zinc.

The preferred pharmaceutically acceptable salts are trifluoroacetate, tosylate, mesylate, and chloride.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for



various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

5       Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Solid form preparations may be converted into liquid preparations shortly before use for either oral or administration. Parenteral forms to be injected intravenously, intramuscularly or subcutaneously are usually in the form of sterile solutions and may contain tonicity agents (salts or glucose), and buffers. Opacifiers may  
10       be included in oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

15       Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g., nitrogen.

20       Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

25       The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

30       Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

      The effective amount or therapeutically effective amount of compound of the present invention in a unit dose of preparation may be varied or adjusted from about 1



mg to about 1600 mg per day, preferably from about 1mg to about 1200 mg per day, or about 300 mg to about 1200 mg per day, more preferably from about 1 mg to about 800 mg per day, or about 400 mg to about 800 mg per day and most preferably from about 1 mg to about 100 mg per day from about 400 mg to about 600 mg per day, in single or  
5 divided doses, according to the particular compound and particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience,  
10 the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the  
15 judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. The dose of the preferred compounds of formulas I - IV should be chosen to provide steady state plasma concentrations of ribavirin in the range of about 0.1 ug/mL to about 100 ug/mL, preferably in the range of about 0.1 ug/mL to about 50 ug/mL, more preferably in the range of  
20 about 1 ug/mL to about 3 ug/mL., and most preferably in the range of about 1.8 ug/mL to about 2.6 ug/mL. Plasma ribavirin concentrations may be determined using high pressure liquid chromatographic material with tandem mass spectrometric detection. The method was validated with respect to linearity, selectivity, precision, accuracy and has a limit of quantitation of 50 microg/mL. A typical recommended daily dosage  
25 regimen for oral administration can range from about 1 mg/kg/day to about 100 mg/kg/day, in two to four divided doses.

30

#### General Synthetic Preparation



Ribavirin, 1- $\beta$ -D-ribofuranosyl-1H-1, 2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

5

The ribavirin derivatives of formulas I -VIII may be prepared by use of the sequences of steps illustrated in the following Schemes, and in the Examples using the compounds listed hereinafter the Schemes.

10 In Scheme I, compounds of formula I wherein  $R^5=R^{5a}CO-$ ,  $R^3=R^{3a}CO$  and  $R^2=H$  and  $R^5=R^{5a}CO-$  and  $R^2=R^{2a}CO-$  and  $R^3=H$  and  $R^5=R^{5a}CO-$  and  $R^3=R^2=H$ , are prepared. Compound 110 (ribavirin) and benzaldehyde are treated with  $ZnCl_2$  in excess benzaldehyde as solvent at ambient temperature (20 to 25°C) for 24 hrs. to give compound 111. Treatment of 111 with the alkanoyl chloride  $R^{5a}COCl$  in the presence of  
15 base e.g. triethylamine ("TEA"); or with the carboxylic acid ( $R^{5a}COOH$ ) and triethylamine and coupling reagent such as dicyclohexylcarbodiimide ("DCC") produces compound 112. Removal of the acetal protecting group with trifluoroacetic acid:water (9:1,v/v) at ambient temperature for 0.25-  
20 2 hrs, preferably about 0.05 hrs. provides compound 113. Compound 113 is converted into a mixture of compounds 114 and 115 by treatment of 113 with  $R^{3a}COOH$ , base and DCC or  $R^{3a}COCl$  and base, e.g., TEA.

Compounds 114 and 115 may be separated by standard chromatographic techniques to provide pure compounds 114 and 115.

25 In Scheme II, compounds of formula 1 wherein  $R^5=R^3=H$  and  $R^2=R^{2a}CO-$  are prepared from compound 110 (ribavirin). Compound 110 is treated with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane, i.e.,  $[(i-Pr)_2SiCl]_2O$ , in DMF as solvent in the presence of imidazole for 1-4 hrs. at ambient temperature to give compound 116. Treatment of 116 with  $R^{2a}COCl$  and base e.g., TEA or  $R^{2a}COOH$ , base and a coupling reagent e.g., DCC for 12-48 hrs. at ambient  
30 temperature provides 117. Treatment of 17 with  $Bu_4NF$  in tetrahydrofuran ("THF") at ambient temperature for 1-10 hrs. provides compound 118.

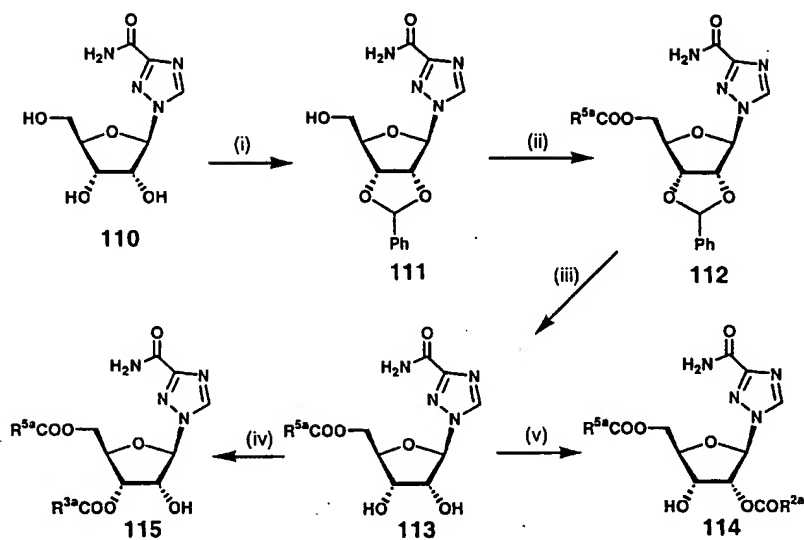


Scheme III illustrates the preparation of the compounds of formula I wherein  $R^5=R^2=H$  and  $R^3=R^{3a}CO-$  and  $R^5=R^3=H$  and  $R^2=R^{2a}CO-$ . Ribavirin is treated with trityl chloride or  $[MeOC_6H_4(C_6H_5)_2]CCOCl$  and base, e.g., pyridine in a solvent DMF at ambient temperature for 6-24 hrs. to provide 119. Treatment of 119 with  $R^{2a}COCl$  and  
5 base or  $R^{2a}COOH$ , base and a coupling reagent, e.g., DCC, provides a mixture of compounds 120 and 121. The mixture is separated into the pure compounds by standard chromatographic techniques. Treatment of 120 or 121 with para-toluenesulfonic acid ("p-TsOH") in methanol in the presence of hydrogen and a palladium on charcoal catalyst at ambient temperature for 2-48 hrs. removes the  
10 protecting group to give 122 and 123, respectively. p-TsOH salt thereof.

Scheme IV illustrates preparation of the compounds of formula I wherein  $R^5=R^{5a}CO-$  or  $R^5=R^{5a}$  and  $R^3=R^2=H$ . Treatment of ribavirin 110 with  $R^{5a}COON=C(CH_3)_2$  in the presence of an enzyme, such as Novo SP 435 lipase at 65°C in a solvent such as  
15 THF or dioxane for 12-48 hrs selectively adds  $R^{5a}CO$  to the form compound 124. See also Examples 9 to 14.



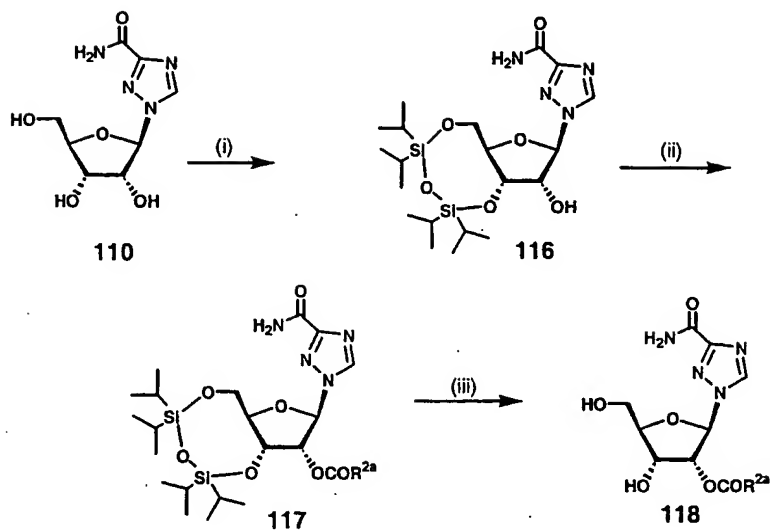
Scheme I (5'-Substitutions)



**Reagents:** (i)  $\text{ZnCl}_2$ ,  $\text{PhCHO}$ , (ii)  $\text{R}^{5a}\text{COCl}$ ,  $\text{Et}_3\text{N}$ ; or  $\text{R}^{5a}\text{COOH}$ ,  $\text{Et}_3\text{N}$ , coupling reagent, (iii)  $\text{TFA-H}_2\text{O}$  (9:1), (iv)  $\text{R}^{3a}\text{COOH}$  or  $\text{R}^{3a}(\text{W})\text{xCOOH}$ , coupling reagent, base; or  $\text{R}^{3a}\text{COCl}$ , or  $\text{R}^{3a}(\text{W})\text{xCOCl}$ , base, (v)  $\text{R}^{3a}\text{COOH}$ , coupling reagent, base; or  $\text{R}^{3a}\text{COCl}$ , base



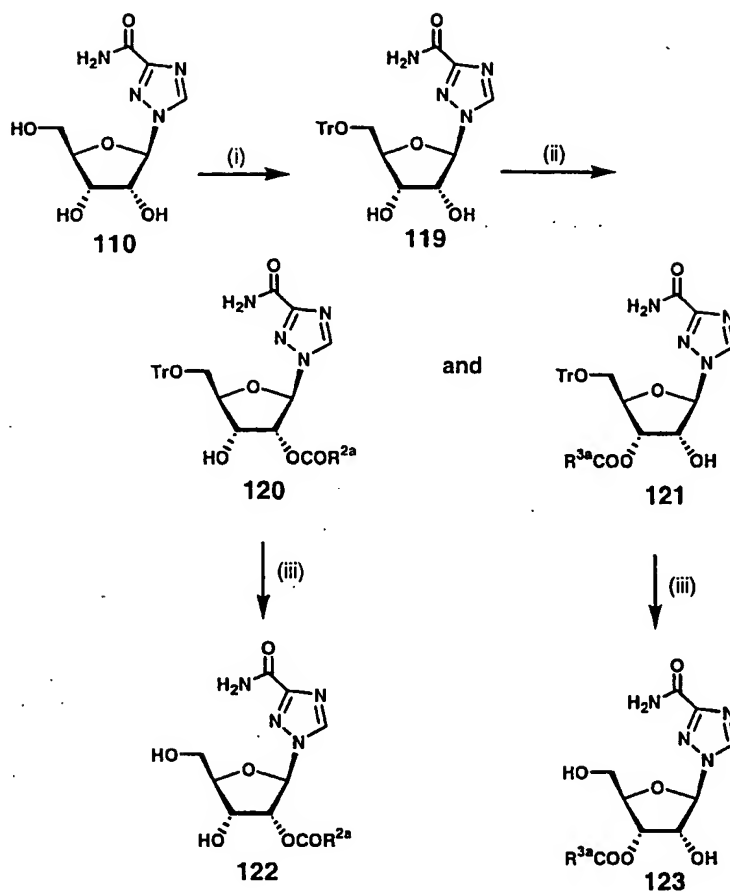
Scheme II (2'-Substitutions)



**Reagents:** (i)  $[(t\text{-Pr})_2\text{SiCl}]_2\text{O}$ , imidazole, DMF; (ii)  $\text{R}^{2a}\text{COCl}$ , base; or  $\text{R}^{2a}\text{COOH}$ , coupling reagent, base; (iii)  $\text{Bu}_4\text{NF}$ , THF



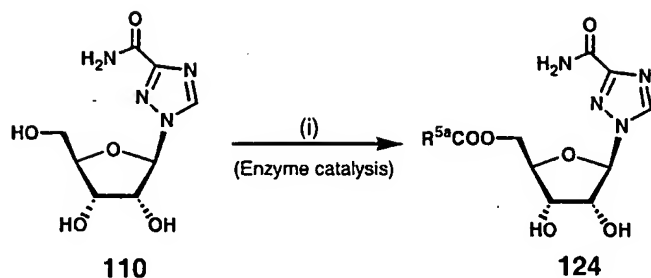
Scheme III (2' and 3'-Substitutions)



**Reagents:** (i) TrCl, base; (ii)  $R^{2a}COCl$ , base; or  $R^{2a}COOH$ , base, coupling reagent; (iii) TsOH, MeOH,  $H_2$ , Pd/C

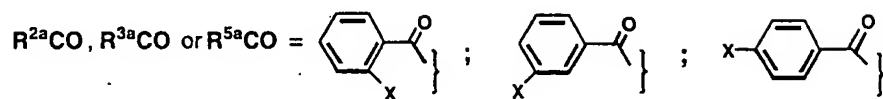


## Scheme IV (5'-Substitutions)

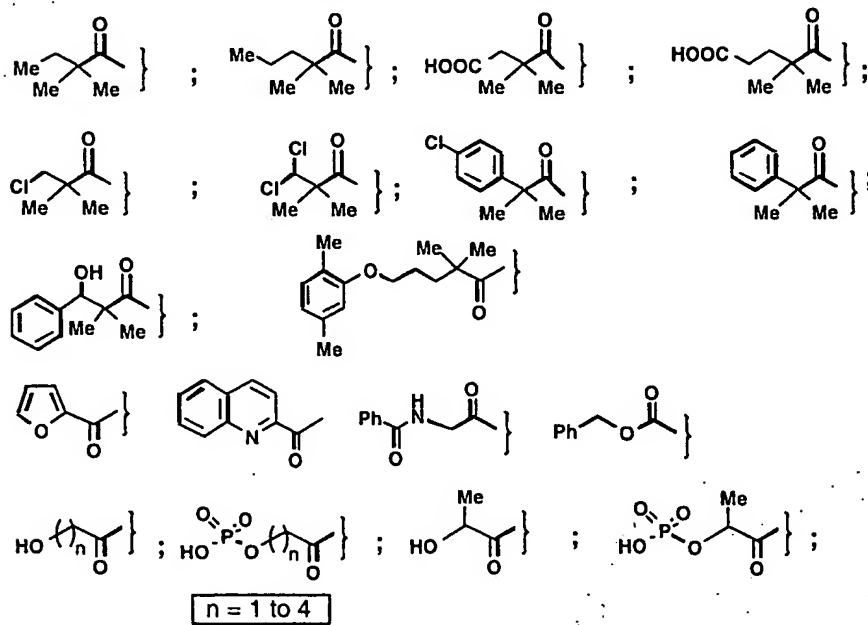


Reagents: (i)  $R^{5a}COO-N(CH_3)_2$ , SP435 lipase, 65°C, THF

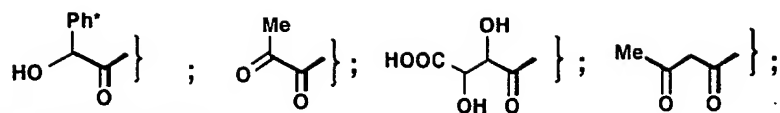
Examples for all schemes:



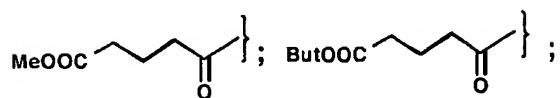
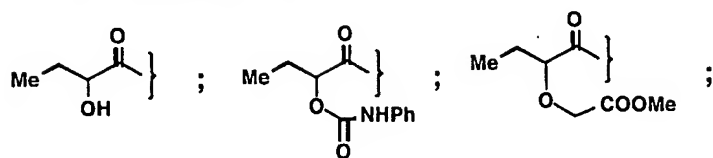
X = OH, OAc, NH<sub>2</sub>, NHCbz, OMe, CN, NO<sub>2</sub>, F, Cl, Br, and disubstituted benzoates with a combination of these groups 'X'.





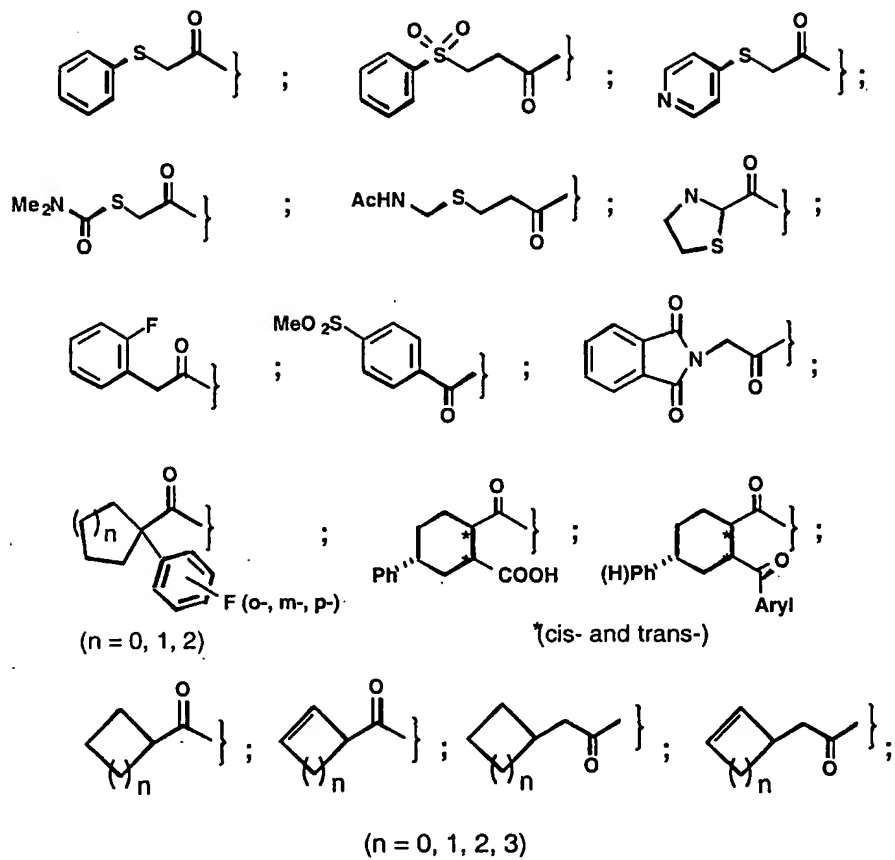


\*(and substituted Ph)

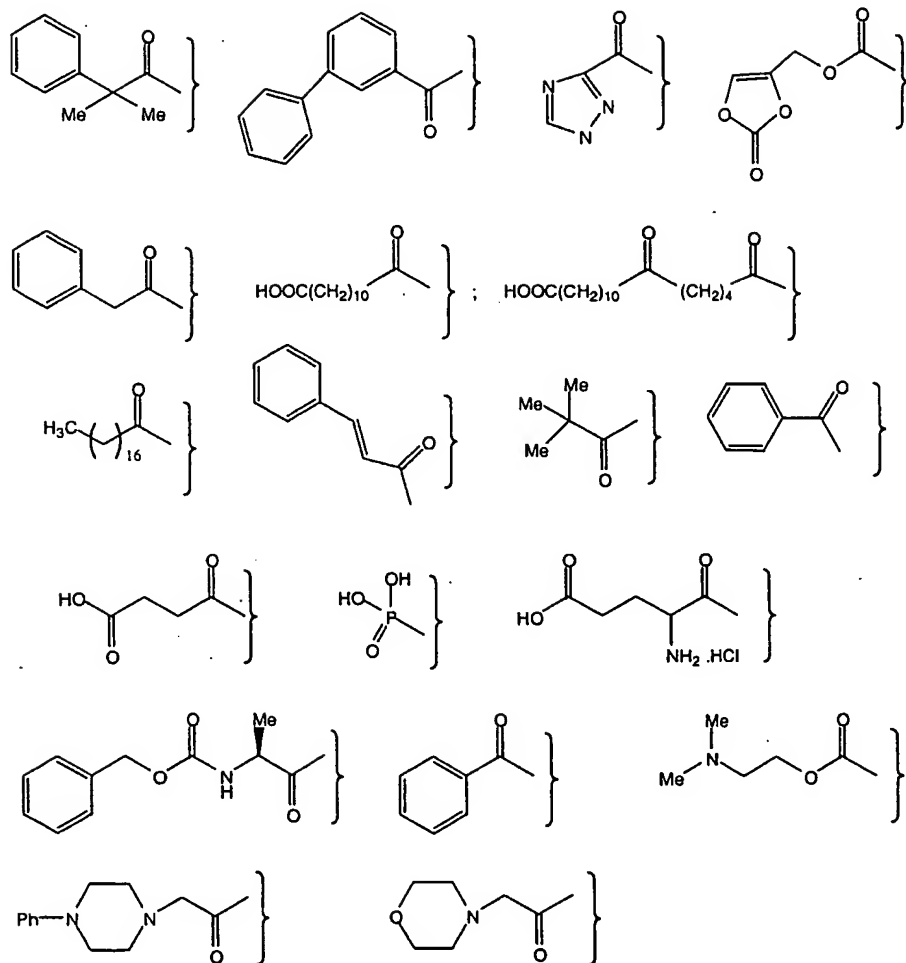


(and 5'----> 3' cyclic diester)



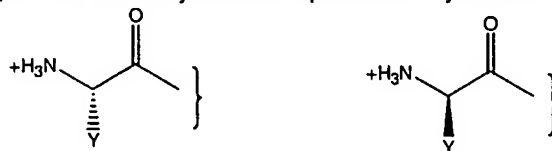




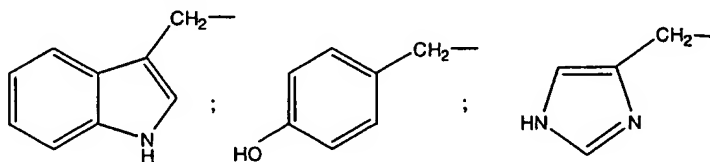




$R^{2a}CO$ ,  $R^{3a}CO$ , and  $R^{5a}CO$  may also be represented by the formulas:

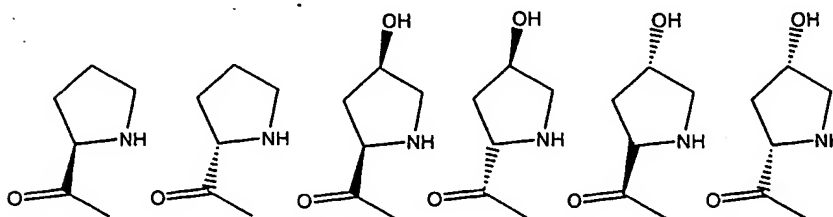


$Y = H, CH_3; CH_3CH_2-; CH_3CH_2CH_2-; Me_2CH-; Me_2CH_2CH_2-; CH_3CH_2CH(Me)-$   
 $PhCH_2-; HOOCCH_2CH_2-; HSCH_2-; HOOCCH_2-; MeSCH_2CH_2-; HOCH_2-;$



or  $Y$  is  $H_2N(CH_2)_4-$  or  $CH_3CH(OH)-$ ; or a pharmaceutically acceptable salt thereof;

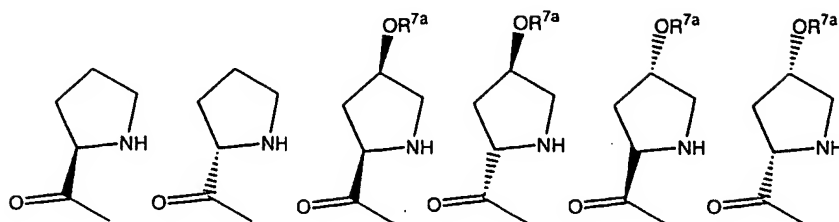
or  $Y$  taken together with the  $\alpha$  carbon and N form



5 or a pharmaceutically acceptable salt thereof.



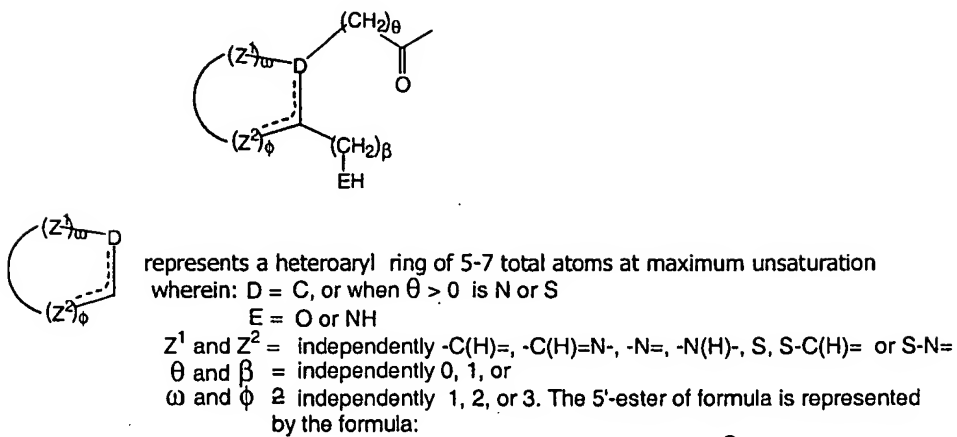
or Y taken together with the  $\alpha$  carbon and N form



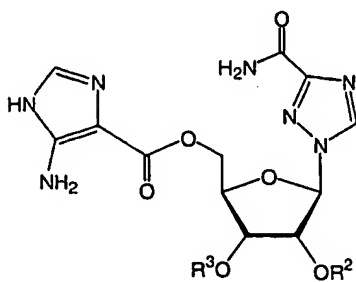
wherein R<sup>7a</sup> is as defined above;  
or a pharmaceutically acceptable salt thereof.



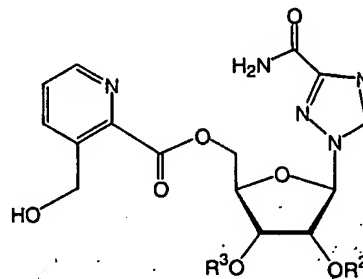
Exemplary 5'- heteroaryl esters of Formulas I & II wherein  $R^5 =$



The following 5' esters may be prepared as described in Schemes hereinabove, using appropriately protected acids which are readily obtained by procedures well known to one skilled in the art.



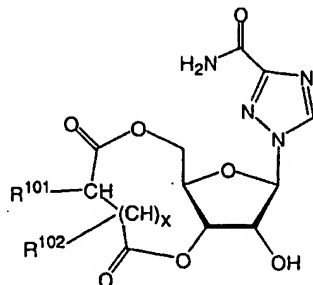
D = C, E = NH,  $Z^1 = (-CH=N-)$ ,  $\omega = 1$ ,  
 $Z^2 = -NH-$ ,  $\phi = 1$ ,  $\theta = 0$ , and  $\beta = 0$



D = C, E = O,  $Z^1 = (-CH=N-)$ ,  $\omega = 1$ ,  
 $Z^2 = -CH=$ ,  $\phi = 2$ ,  $\theta = 0$ , and  $\beta = 1$

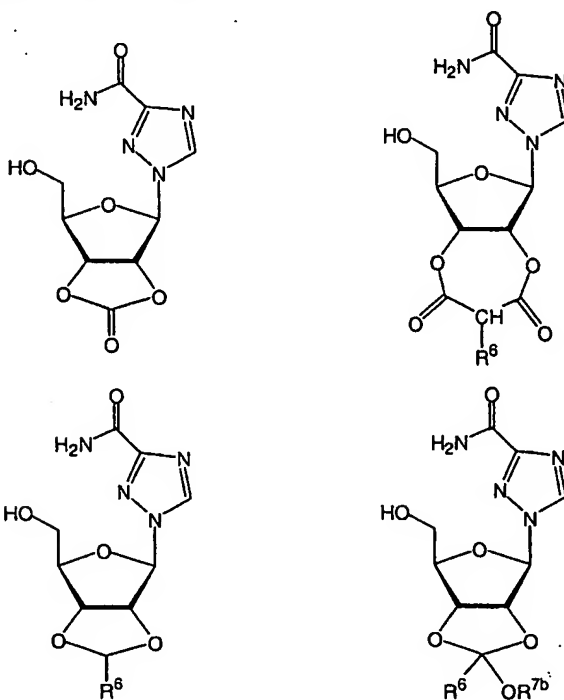


The following 5'-3' cyclic ester (Formula I wherein  $R^2=H$ ) may be prepared using the Schemes herein above and readily available starting materials.



wherein  $R^{101}$  and  $R^{102}$  are independently H, alkanoyloxy,  $OR^{7b}$  or  $NR^6R^{7b}$  and  $x=1$  or  $2$

The following 3'-2' cyclic esters (formula I wherein  $R^5=H$ ) may be made using the Schemes herein above and readily available starting materials.

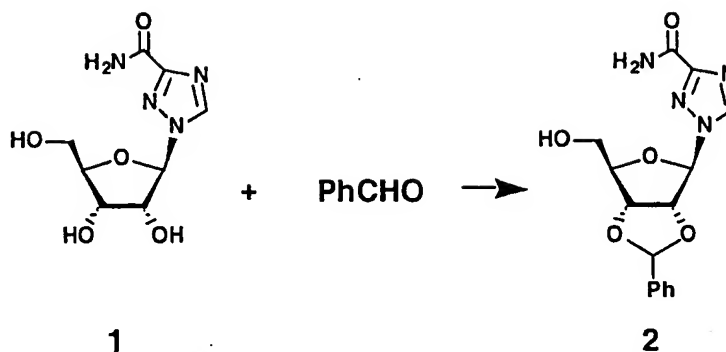




5

Example I

A.



10

A.-Benzylidene ribavirin

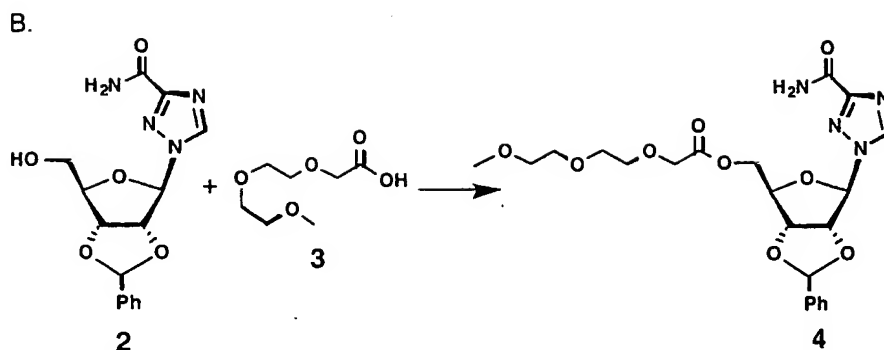
15

20

Combine 20 g ribavirin (1, 87 mmol), 200 ml of benzaldehyde, and 20 g of  $\text{ZnCl}_2$ . Stir the so-formed reaction mixture at ambient temperature for 24 hours. Pour the resulting solution, with stirring, into 2.5 L of ethyl ether ( $\text{Et}_2\text{O}$ ). Suction-filter the resulting mixture and dry the solid precipitate. Mix the solid precipitate with 1.2 L of ice-cold 2N sodium hydroxide (NaOH) solution. Extract the mixture with 2x0.75L of cold ethyl acetate ( $\text{EtOAc}$ ) and wash the organic layer with brine. Gravity-filter the organic layer through fluted filter paper, then concentrate it in vacuo to leave a solid. Triturate the solid thoroughly with 0.5 L of  $\text{Et}_2\text{O}$ , suction-filter and wash the so-formed precipitate with fresh  $\text{Et}_2\text{O}$  to leave 23 g of compound 2 as a solid; Calc. for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_5$  (332.32). MS(FAB) = 333.1.

25





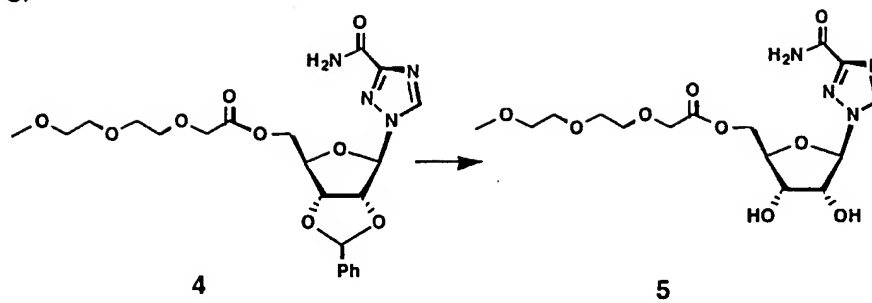
10 Combine 0.5g (2.8 mmol) of compound 2 from step A, 0.80g(2.4 mmol) of compound 4  
[MeO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H] and 0.8 g (1.2 mmol) of 4-(N,N-dimethylamino)pyridine  
(DMAP) in 15 ml of N,N-dimethylformamide (DMF). Add 2.5 ml of a 1M solution of  
dicyclohexylcarbodiimide (DCC) in dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), and stir the resulting  
mixture at ambient temperature for 0.5 hour. Heat the so-formed reaction mixture at 100  
15 °C for 1 hour. Quench the reaction mixture with aqueous 5% KH<sub>2</sub>PO<sub>4</sub>, and extract it  
with 2x100 ml of ethyl acetate (EtOAc). Wash the organic extract with 20 ml cold water,  
then with saturated brine. Gravity-filter the organic extract through fluted filter paper,  
then concentrate the filtrate *in vacuo* to leave a gum residue. Purify the residue by  
column chromatography (silica gel, gradient of 1% to 6% methanol-CH<sub>2</sub>Cl<sub>2</sub>) to give 0.48  
20 g of compound 4; Calc. for C<sub>22</sub>H<sub>28</sub>N<sub>4</sub>O<sub>9</sub> (492.49); MS(FAB) = 493.1.

25

30



C.



10

C. Treat 0.45 g 4 (0.91 mmol) with 10 ml of trifluoroacetic acid (TFA)-water (9:1 v/v) at ambient temperature for 0.5 hour. Quench with 30 ml xylene, then concentrate the so-formed mixture *in vacuo* to leave a gum. Triturate the gum with EtOAc, dilute with Et<sub>2</sub>O, then suction-filter and dry the gum to leave 0.23 g of compound 5 as a solid, Calc.

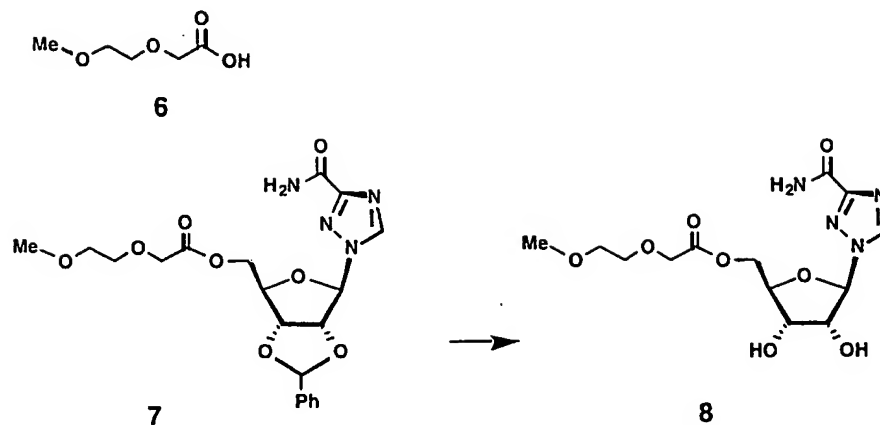
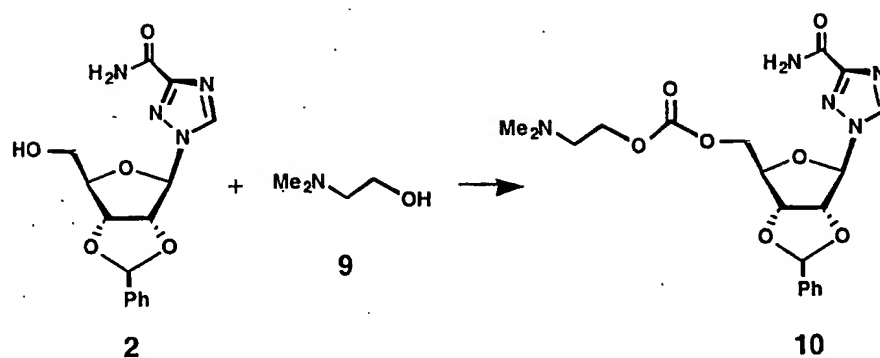
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C<sub>15</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub> (404.38); MS(FAB) = 405.1.

### Example 2

Follow the procedures of Example 1A and 1B except substitute an equivalent amount of the compound 6 (MeOCH<sub>2</sub>CH<sub>2</sub>OCHCO<sub>2</sub>H) for compound 3 in step B to form compound 8. Follow the procedures of step C of Example 1 except substitute an equivalent amount of compound 7 for compound 4 to form the compound 8.

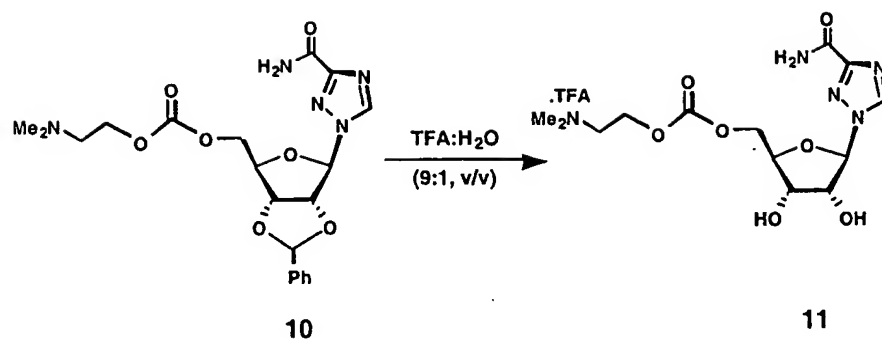


Example 3

- A. Treat a solution of 0.32 g (3.6 mmol) of compound 9 [2-(N,N'-dimethylamino)ethanol] in 10 mL of N,N-dimethylformamide (DMF) at 5°C with 0.58 g carbonyldiimidazole (3.6 mmol), and allow the so-formed solution to warm to 20°C over 0.5 hr. Add to the resulting reaction mixture 0.8 g (2.4 mmol) of compound 2 prepared in accordance with Example 1A and stir the so-formed reaction mixture at ambient temperature for 24 hr. Concentrate the mixture *in vacuo*, add 50 mL of ethyl ether, and allow the so-formed mixture to set for 24 hr. Decant the supernatant solution, and purify the residue by column chromatography (silica gel, gradient of 10% to 20% methanol-tetrahydrofuran) to give 0.21 g of compound 10; calc.  $C_{20}H_{25}N_5O_7$ , (447.44); MS(FAB) = 448.1.

B

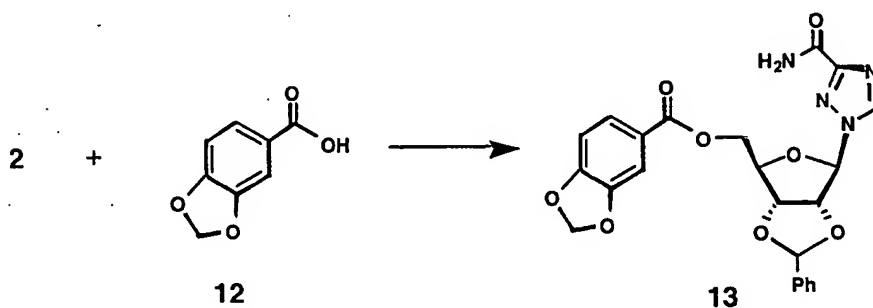




Follow the procedures of Example 1C except substitute an equivalent amount of compound 10 for compound 4 to obtain compound 11.

#### Example 4

10 A.

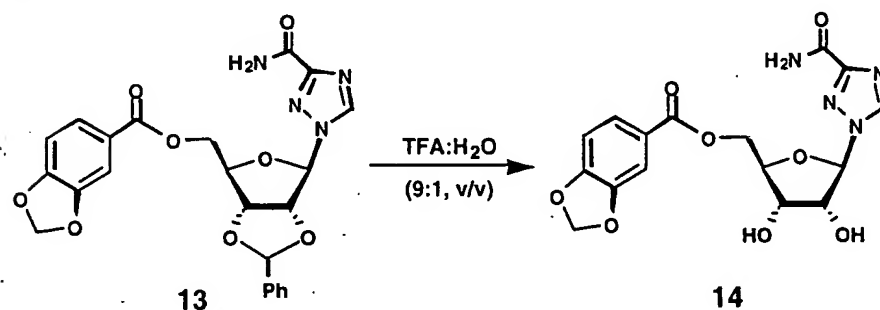


A stirred, dry DMF (5mL) solution of 500 mg (1.506 mmol) of compound 2 prepared in accordance with the procedures of Example 1A, 300 mg (1.2 eq) of piperonylic acid (compound 12) was treated at ambient temperature with 732 mg (1.1eq) of benzotriazolyloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP reagent") and 576 $\mu$ L (2.2 eq) of Hunig's base, i.e., -diisopropylethyl amine, [(i-Pr)<sub>2</sub>NEt], under a nitrogen atmosphere. The so-formed reaction mixture was stirred overnight at ambient temperature. Thin layer chromatography (TLC) showed one major new spot. The reaction mixture was quenched with an aqueous NH<sub>4</sub>Cl solution and



diluted with EtOAc. The organic layer was washed with water and brine and then dried over  $\text{Na}_2\text{SO}_4$ . The organic solvent was evaporated to produce a crude purple solid. The crude solid was purified on a silica gel chromatography column with 2-3%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  as an eluent. The appropriate fractions were combined to give 550 mg of compound 13 as a purple-tinted solid (76% yield). The  $^1\text{H}$  nmr spectrum (350 MHz in  $\text{CDCl}_3$ ) was consistent with the structure of 13.

B.



10

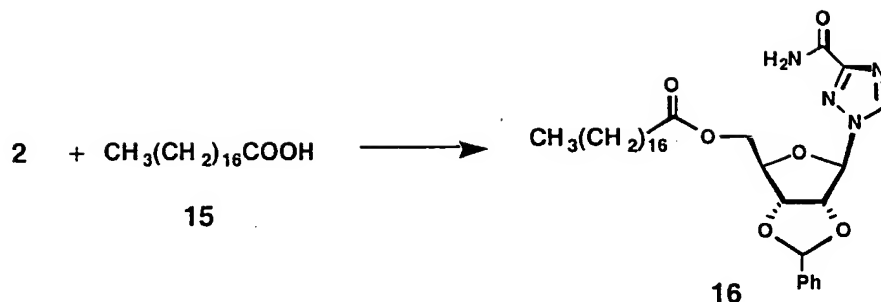
Compound 13 from step A was treated with 4 mL of TFA:H<sub>2</sub>O (9:1,v/v) for 40 min. at ambient temperature. The solvents were evaporated to give a yellow solid. Water was added and evaporated. The crude solid was dried overnight. To the crude product was added 2 x 4 mL of MeOH. The MeOH layer was yellow. The insoluble material was collected and dried to give 342 mg of compound 14 as a white solid. The  $^1\text{H}$  nmr spectrum was consistent with the structure of 14.

15



**Example 5**

A.

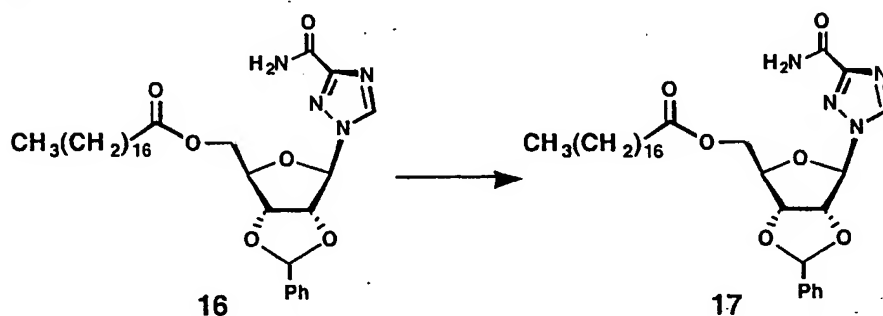


5

To a stirred solution of 500 mg (1.505 mmol) of 2 prepared in accordance with Example 1A in 3 mL of dry DMF at ambient temperature was added 516 mg (1.2 eq) of stearic acid (compound 15), 670 mg (1.0 eq) of the BOP reagent and 792  $\mu\text{L}$  (3.0 eq) of Hunig's base. The so-formed reaction mixture was stirred overnight at ambient temperature. The reaction mixture was isolated in accordance with the procedures of Example 4A to give 595.5 mg of compound 16 as a viscous white solid (66% yield). The  $^1\text{H}$  nmr spectrum was consistent with the structure of 16.

10

15 B.



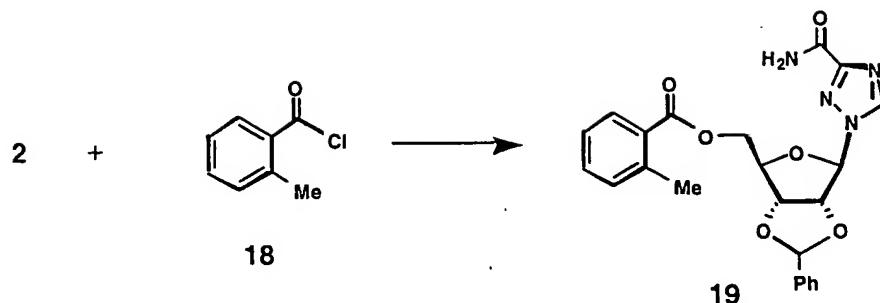
Compound 16 (417 mg, 0697 m mol) was treated in accordance with the procedures of Example 4B to give 330 mg of compound 17 as a white solid (93% yield). The  $^1\text{H}$  nmr spectrum and MS-FAB were consistent with the structure of 17.

20

**Example 6**

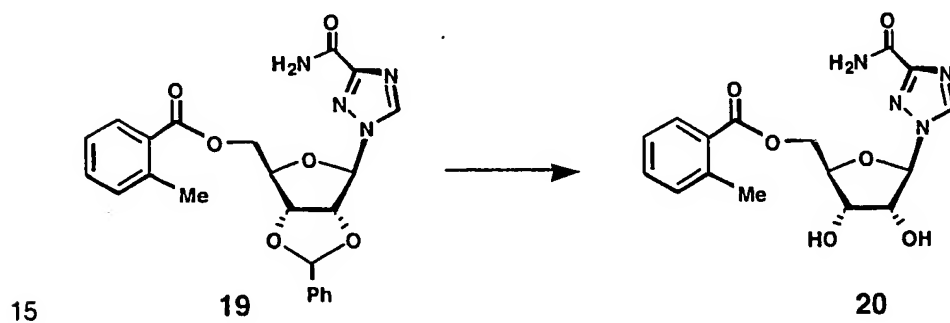


A.



- 5 To a stirred suspension of 332 mg (1.0 mmol) of compound 2 prepared in accordance with Example 1A in 5 ml of dry  $\text{CH}_2\text{Cl}_2$  was added 209  $\mu\text{L}$  (1.5 eq) of triethylamine ( $\text{Et}_3\text{N}$ ) and 167  $\mu\text{L}$  (1.2 eq) of o-toluoyl chloride (compound 18). TLC showed completion of the reaction after the reaction mixture had been stirred at ambient temperature for 4 hours. The so-formed clear reaction mixture was diluted with EtOAc and quenched with water.
- 10 The separated organic layer was washed with water and brine, dried and evaporated to give a crude white solid. The crude solid was purified on silica gel column chromatography eluting with 2-3% MeOH to give 262 mg of compound 19 as a white solid (57% yield).

B.

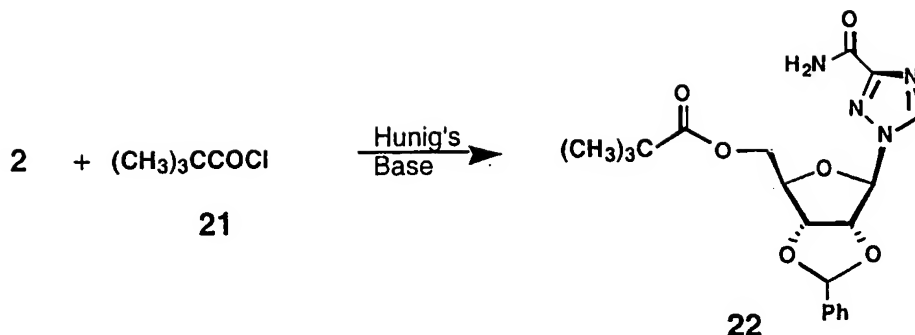


Compound 19 (262 mg) was treated with 3 mL of TFA: $\text{H}_2\text{O}$  (9:1 v/v) in accordance with the procedure of Example 4A to give 210 mg (99% yield) of the compound 20. The  $^1\text{H}$  nmr spectrum was consistent with the structure of compound 20.



Example 7

A.



5

10

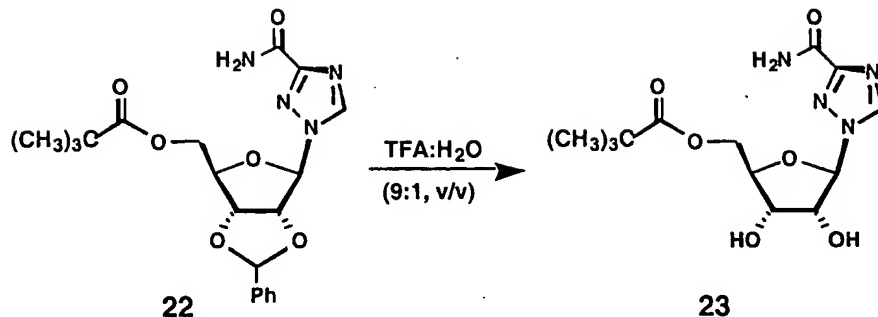
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To a stirred suspension in a reaction flask immersed in an ice bath of 498 mg (1.5 mmol) of 2 prepared in accordance with Example 1A in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, was added 146  $\mu$ L (1.80 mmol, 1.2 eq) of pyridine and 203  $\mu$ L (1.65 mmol, 1.1 eq) of trimethylacetyl chloride (compound 21) at 0°C. The ice bath was removed after 5 min. Stirring was continued for 30 min. and 1 mL of DMF was added; the mixture changed from a suspension to a cloudy solution. By TLC, there was a substantial amount of unreacted starting material (compound 2). The reaction mixture was stirred overnight, and an additional amount of compound 21 (203  $\mu$ L, 1.1 eq) and 180 mg (1.5 eq) of DMAP were added. The so-formed reaction mixture was stirred for 4 days at ambient temperature. There was still some unreacted starting material (compound 2) by TLC. The reaction mixture was worked-up by routine extraction between H<sub>2</sub>O/EtOAc. The crude product was purified by silica gel column chromatography eluting with 2-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give 411.3 mg of compound 22 (66% yield) as a white solid.

B.



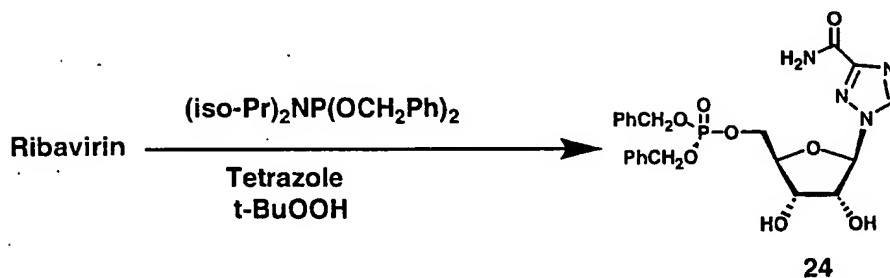


Compound 22 (316 mg) was treated with 4 mL of TFA:H<sub>2</sub>O (9:1 v/v) in accordance with the procedures of Example 4B to give 265 mg of compound 23.

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### Example 8

A.

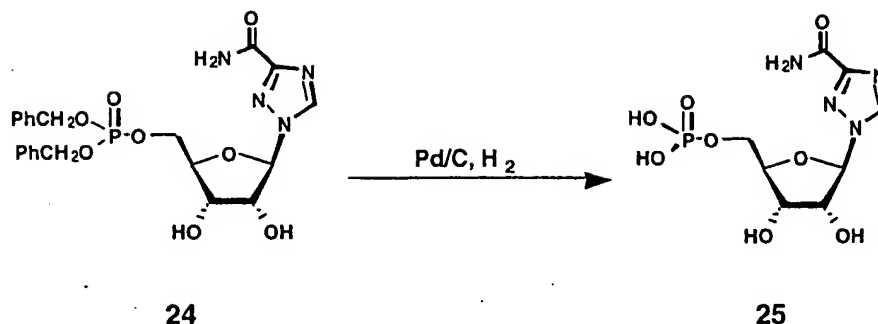


To a stirred mixture of 500 mg (2.1 mmol) of ribavirin and 2.07 g (1.04 mL, 1.5 eq, 3.1 mmol) of N,N-disopropyl-dibenzyl phosphoramidate in 5 mL of DMF at room temperature, was added 433 mg (6.1 mmol, 3 eq) of tetrazole. The resulting reaction mixture was stirred at room temperature for 2 hrs. , and then 1.11 mL (3 eq) of tert-butylperoxide (5.5M in decane) were added. The so-formed reaction mixture was stirred for 2 hrs. Water was added and the organic layer was washed, dried and evaporated to give a crude product. The crude product was purified on silica gel column chromatography using MeOH/CH<sub>2</sub>Cl<sub>2</sub> as an eluent to give 493 mg of compound 24 as white solid.

FAB:MS:MH<sup>+</sup>=505.2.

B.

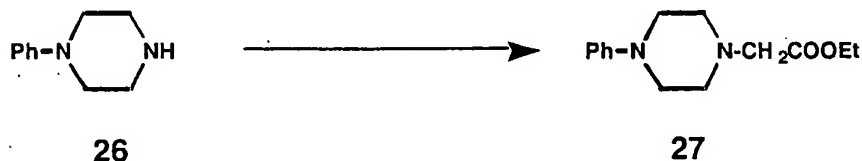




A suspension of compound 24 (278 mg) in a mixture of 3 mL of MeOH and 3 mL of water and 150 mg of 10% Pd on carbon was placed under an atmosphere of hydrogen for 4 hrs. The suspension was filtered through a pad of celite and the solid was washed thoroughly with MeOH. The combined filtrates were concentrated under reduced pressure to give 169.3 mg of the compound 25 as a white solid. FAB-MS,  $MH^+ = 325.1$

#### Example 9

A.

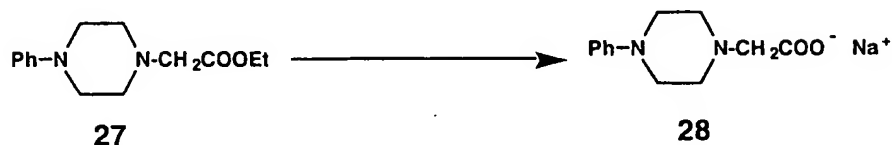


An oil dispersion of NaH (0.88 g of NaH, 0.022 mmol, 1.1 eq) was washed once with dry hexane and then suspended in 10 mL of dry THF. Compound 26 (N-phenylpiperazine, 3.24 g, 20 mmol) was added to the reaction vessel containing NaH in dry THF immersed in an ice bath. The ice bath was removed and the so-formed reaction mixture was stirred for 1 hr. at room temperature. To the stirred white reaction mixture was added 2.66 mL (0.024 mmol, 1.2 eq) of ethyl bromoacetate. The so-formed reaction mixture was stirred overnight. The reaction mixture was cooled to ice bath temperature and quenched with an aqueous  $NH_4Cl$  solution. The so-formed mixture was extracted with EtOAc and the organic layer was washed with aqueous  $NH_4Cl$  brine and dried. The solvent was removed at reduced pressure to provide a crude product which was purified on a silica gel chromatography column using 20% EtOAc/hexane (v/v) as an eluent to



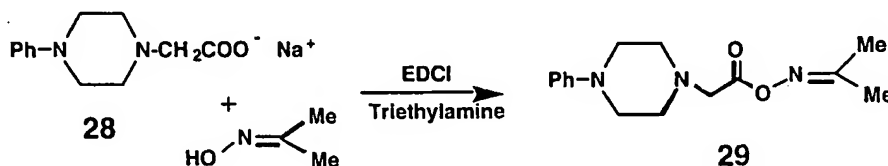
provide 2.10g of compound 27 (ethyl N-phenylpiperazinylacetic acid) as a clear oil. The <sup>1</sup>H nmr spectrum was consistent with the structure of compound 27.

B.



10 To a stirred solution of 2.10g (8.47 m mol) of compound 27 in 8.47 mL of MeOH was added 8.47 mL (1.0 eq) of a 1N NaOH solution. The so-formed reaction mixture was stirred for 3 hrs. at room temperature (no compound 27 was found by TLC). The solvents were removed under reduced pressure to provide a crude product. Water was added to the crude product and the solution was freeze dried overnight to provide 2.10 g of compound 28 as a white solid. The <sup>1</sup>H nmr spectrum was consistent with the structure of compound 28.

C.

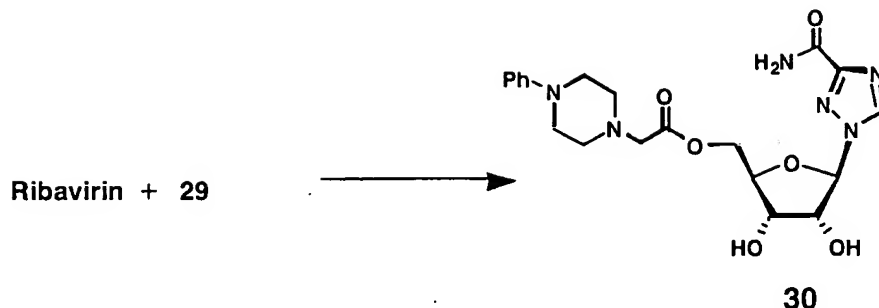


20 To a stirred solution of 1.21g (5.0 m mol) of compound 28 in a mixture of 15 mL of CH<sub>3</sub>CN and 5 mL of DMF was added 1.146g (6.0 m mol, 1.2 eq) of EDC. HCl followed by 837 μL (6.0 m mol, 1.2 eq) of Et<sub>3</sub>N and 731 mg (10.0 mmol, 2 eq) of acetone oxime (compound 28). The so-formed reaction mixture was stirred overnight and then diluted with EtOAc. The organic layer was washed with water and brine, dried and concentrated to give a crude product. The crude product was purified on silica gel column chromatography using 20% EtOAc/hexane (v/v) as an eluant to give 237 mg of compound 29 as a white solid. The <sup>1</sup>H nmr spectrum of the oxime ester was consistent with the structure of compound 29.

25

D.



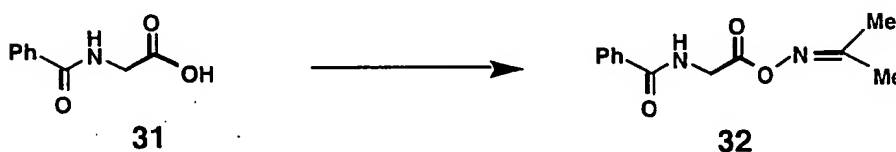


A suspension of 105.0 mg (0.431 m mol) of ribavirin 237 mg (0.862 m mol) of oxime ester 29 and 0.1g of Novo SP435 lipase (*Candida antarctica*) in 5 mL of anhydrous THF was stirred at 65°C for 24 hrs. The so-formed reaction mixture was cooled to room temperature, filtered and washed with MeOH. The crude material was purified on silica gel column chromatography using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (v/v) as eleunt to produce 66 mg of Compound 30 (a white solid) as a single product (in 42% yield). No other product was observed by TLC. The <sup>1</sup>H nmr spectrum (300 MHz, DMSO-d<sub>6</sub>) was consistant with the 5' ribavirin ester of structure 30.

10

Example 10

A.

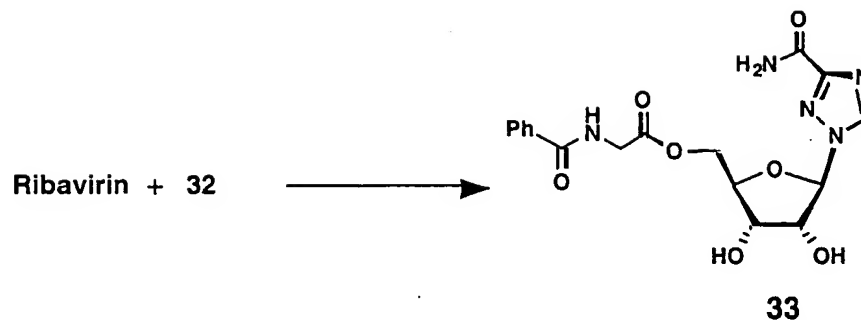


To a stirred solution of 2.45 g (1.4 mmol) of hippuric acid (compound 31) and 1.00 g (1.0 eq) of acetone oxime in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> at room temperature was added 2.83 g (1.0 eq) of DCC. The so-formed reaction mixture was stirred overnight and then filtered. The filtrate was concentrated under reduced pressure to produce a residue which was purified with EtOAc/hexane to give 2.36 g of the acetone oxime ester (32) as a colorless oil. The FAB-MS: MH<sup>+</sup> = 235.1.

20

B.

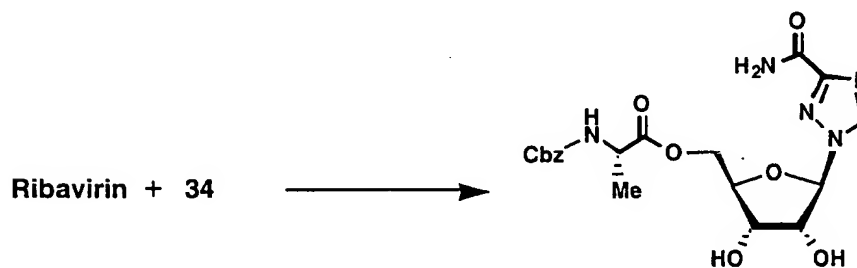




The procedure of Example 9, Step D was used except 2.13 g (9 mmol) of compound 32 was substituted for compound 29, 0.734 g (3 mmol, 1/3 eq) of ribavirin and 0.6 g of SP435 lipase were used in 25 ml of THF. The crude product was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ : MeOH (20:1, v/v) as an eluent to provide a crude product. The crude product was crystallized from MeOH:  $\text{Et}_2\text{O}$  to provide 0.936 g of compound 33. FAB:MS,  $\text{MH}^+=406.1$ .

#### Example 11

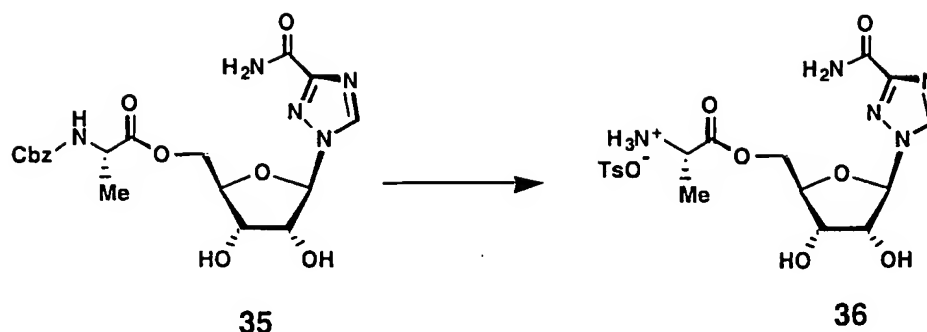
A.



Compound 34, the acetone oxime ester of Cbz-L-alanine, was prepared in accordance with the procedures of F. Morris and V. Gotor, *Tetrahedron*, **1994**, 50, 69-6934 at paragraph bridging 6932-6933.. Then, the procedure of Example 10, Step B, was followed using 1.00 g (3.6 mmol) of compound 34 in place of compound 32, 0.294 g (1.2 mmol) of ribavirin, and 0.48 g of Novo SP435 lipase in 12 ml of THF. The crude produce was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ : MeOH (20:1, v/v) as an eleunt to give 0.660 g of compound 35 as a white solid. The white solid was recrystallized from MeOH-EtOAc to give 0.532 g of compound 35.



C.

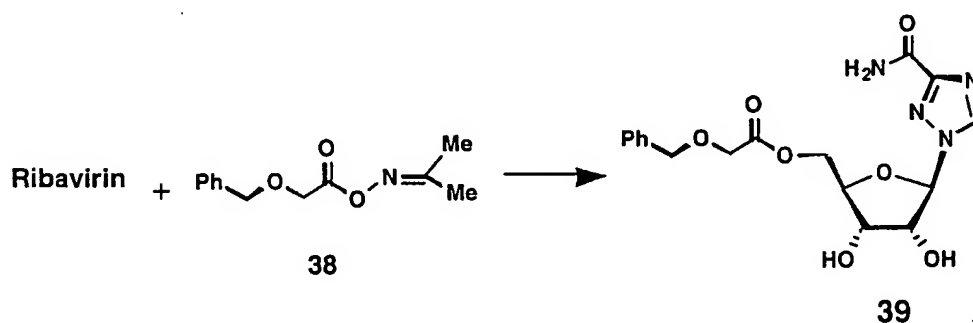


5 To a mixture of 0.100 g (0.222 mmol) of compound 35 and 42.3 mg (1 eq) of TSOH.H<sub>2</sub>O in 3 ml of aqueous MEOH was added 50 mg of 10% Pd on carbon. The resulting black suspension was placed under a hydrogen atmosphere for 4 hours. The so-formed reaction mixture was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrates were concentrated and the solvent removed to give 0.101 g of compound 36 as a white solid. FAB:MS MH<sup>+</sup>=316.1.

10

### Example 12

A.



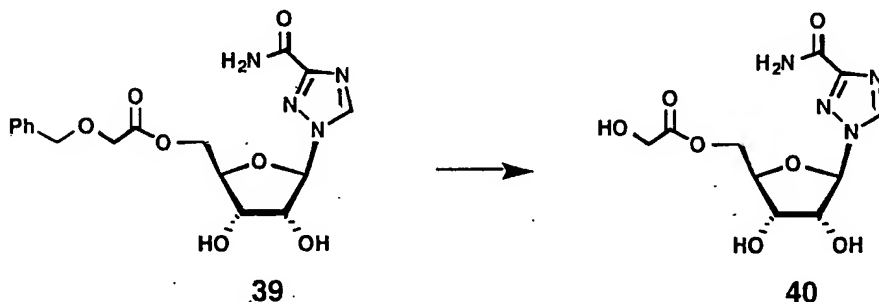
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Compound 38 (PhCH<sub>2</sub>OCH<sub>2</sub>COO-N=C(CH<sub>3</sub>)<sub>2</sub>) was prepared from 2.17 ml (2.53 eq) benzyloxyacetylchloride (Compound 37) and 1.00 g of acetone oxime in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> containing 1.67 g (1 eq) of DMAP in accordance with the procedure of Example 10 Step A. Then, the procedure of Example 10, Step B was followed using 2.40 g (10.8



mmol) of compound 38 in place of compound 32 1.325 g (5.4 mmol) of ribavirin 2.18 g of Novo SP435 lipase in 70 ml of THF. The mixture was treated overnight at 70°C under a nitrogen atmosphere. The crude product was purified on silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>:MeOH (10:1, v/v) as an eluent to provide 0.511 g of a mixture of two compounds. The desired compound 39 was purified by crystallization from MeOH:Et<sub>2</sub>O to give 0.367 g of compound 39 as a white crystalline product.

B.

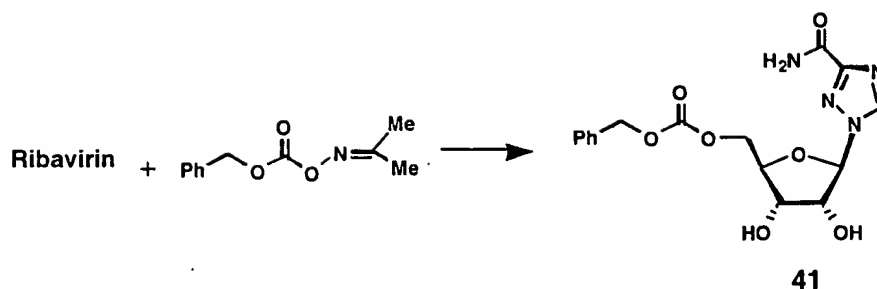


10

To a stirred suspension of 0.200 g of compound 39 in 5 ml of MeOH containing 50 mg of palladium black under an atmosphere of nitrogen was added 0.20 ml of formic acid. The resulting reaction mixture was heated to reflux for 1 hour. The resulting reaction mixture was cooled and filtered through a pad of cotton wool. The solids were thoroughly washed with methanol and then water. The combined filtrates were concentrated under reduced pressure to give a residue. Methanol was added to provide 99.2 mg of the compound 40. FAB-MS:MH<sup>+</sup>= 303.1.

15



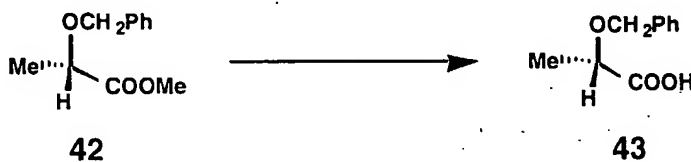
Example 13

Compound 40 ( $\text{PhCH}_2\text{OCOO-N}=\text{C}(\text{CH}_3)_2$ ) was prepared in accordance with the procedure of Step A of Example 10. Then the procedure of Step B of Example 10 as followed using 500 mg (2.4 mmol) of compound 40 in place of compound 32, 295 mg (1.2 mmol) of ribavirin, 160 mg of Novo SP435 in 15 ml of THF. The so-formed reaction mixture was heated at  $70^\circ\text{C}$  for 3 days. The crude product dissolved in MeOH was purified on silica gel column chromatography using  $\text{CH}_2\text{Cl}_2$ :MeOH (20:1, v/v) as an eleunt to provide 156 mg of compound 41. FAB:MS,  $\text{MH}^+=379.2$ .

Example 14

A. The benzyl ether of methyl-L-lactate (compound 42) was prepared from methyl-L-lactate in accordance with the procedures of U. Widner Synthesis 1987, 568.

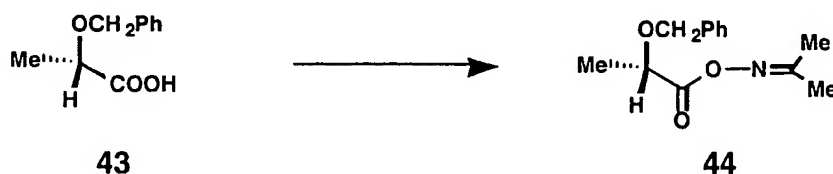
20 B.





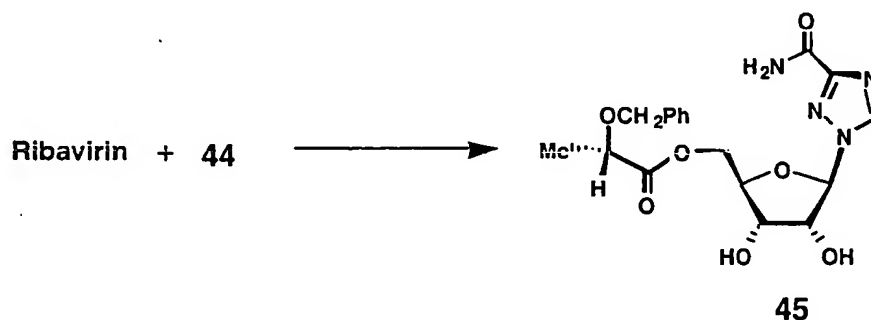
To a stirred solution of 1.00 g of compound 42 in a mixture of 9 ml of MeOH and 3 ml of water was added 216 mg (1 eq) of LiOH.H<sub>2</sub>O. The so-formed reaction mixture was stirred for 4 hours. The resulting mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The aqueous phase was separated, washed with CH<sub>2</sub>Cl<sub>2</sub> and acidified with excess 10% aqueous HCl. The organics were extracted with EtOAc. The EtOAc layer was dried and concentrated to give 779 mg of compound 43 as a colorless oil.

C.



The procedures of Step A of Example 10 were followed using 1.15 g (6.39 mmol) of compound 43 in place of compound 31, 513 mg, (7.03 mmol, 1.1 eq) of acetone oxime, 1.45 g of DCC in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> to produce 1.20 g of the acetone oxime ester, compound 44.

D.

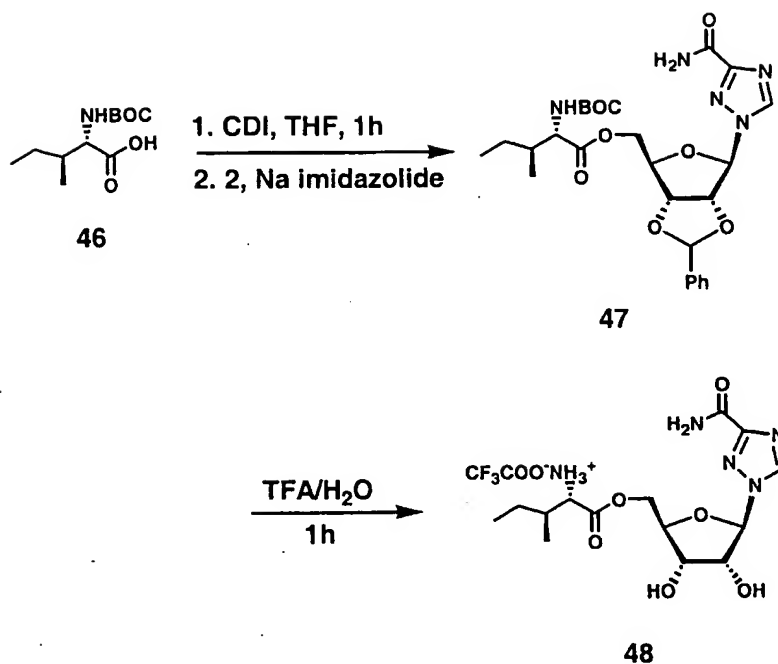


The procedure of Step B of Example 10 was followed using 1.2 g (5.1 mmol) of compound 44 in place of compound 32, 600 mg (2.5 mmol) of ribavirin and 500 mg of Novo SP435 lipase in 20 ml of THF. The mixture was washed at 70°C until no starting found by TLC.

The crude reaction product was purified by silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>:MeOH (20:1, v/v) to produce 183 mg of compound 45 as a white solid.



## Example 15



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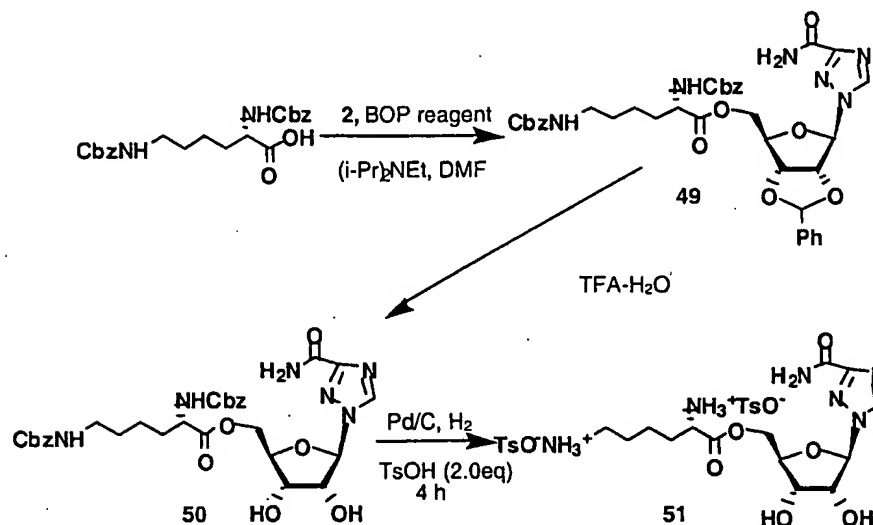
A solution of N-t-Boc-L-isoleucine (available from Sigma Chemical Co. St. Louis, Mo) (1.270 g, 5.5 mmol) in anhydrous THF (30mL) was treated with CDI, i.e., carbonyl-diimidazole (981 mg, 6.05 mmol) at room temperature for 1 hr. The compound 2 of Example 1 (1.660 g, 5.00 mmol) and sodium imidazolidine (150 mg, 1.5 mmol) were then added to the reaction mixture. This mixture was heated at 45°C for 20 hrs. The reaction was diluted with EtOAc and quenched with aqueous NH<sub>4</sub>Cl. The organic layer was washed with water three times and once with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The dried organic layer was filtered and the filtrate was concentrated to give an off white solid which was purified on silica gel column chromatography (5-10% by volume of MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 1.244 g of compound 47.

15



Compound 47 was treated with trifluoroacetic acid (TFA)/ water (9:1 v/v) at room temperature for 1 hr. All volatiles were evaporated. Water was added and evaporated again to afford 1.10 g of compound 48 as a soft solid. MS(FAB)=358 (MH<sup>+</sup>, 100%).

5

Example 16

A solution of N,N-diCbz-L-lysine (available from Sigma Chemical Co. St. Louis, Mo) (749 mg, 1.81 mmol) and compound 2 (500 mg, 1.506 mmol) in anhydrous DMF (5 mL) was treated with (732 mg, 1.66 mmol) of benzotriazolyloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP reagent" available from Sigma Chemical Co. St. Louis, Mo) followed by 576 mL, 3.31 mmol of Hunig's base, i.e., N,N-diisopropyl-ethyl amine, [ "(i-Pr)<sub>2</sub>NEt " available from Aldrich Chemical Co., Milwaukee, WI ] under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and quenched with aqueous NH<sub>4</sub>Cl. The organic layer was washed three times with water, once with brine, and dried over Na<sub>2</sub>SO<sub>4</sub> and . The dried organic layer was filtered and the filtrate was concentrated to give compound 49 as an off white solid .

20

Compound 49 was treated with trifluoroacetic acid/ water (9:1 v/v) at room temperature for 1 hr. All volatiles were evaporated. Water was added and evaporated



again to afford the crude product which was purified on a silica gel column (10 % by volume of MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 520 mg of compound 50 as a white solid.

A solution containing compound 50 (140 mg, 0.219 mmol) and p-toluenesulfonic acid monohydrate, TsOH  $\cdot$   $\text{H}_2\text{O}$  (83 mg, 0.438 mmol) was hydrogenated over 10% Pd/C (50 mg) under  $\text{H}_2$  at a pressure of 1 atm for 4 hr. The catalyst was filtered off through a bed of Celite and washed with methanol-water. The filtrate was evaporated to afford 157 mg of compound 51 as a white powder. MS(FAB)= 373 ( $\text{MH}^+$ , 100%).

#### Example 17

10

Follow the procedures of Examples 11, 15 or 16 except substitute an equivalent amount of the Cbz- or Boc-D- amino acid derivative of the amino acid listed in the left hand column in the Table 3 below for the Boc-L-isoleucine used in Example 15, or the diCbz-L-lysine used in Example 16, or the Cbz-L-alanine used in Example 11 to obtain the compounds of formula I or a pharmaceutical acceptable salt thereof wherein the R is the moiety listed in Table AA herein above

15

#### Example 18

20

The polyethylene glycol conjugates listed in the right hand column of the Table BB below, can readily be prepared and their molecular weight determined by one skilled in the art view of known methods such as described in European Patent Applications EP0236987, EP0510356 and EP 0 809 996 as well as U.S. Patent No. 5,642,575.

25

The starting polyethylene glycols (PEG) and PEG monomethyl ethers of various molecular weights e.g. 750, 1900, 5000, 10,000 can readily be prepared by methods known in the art or can be obtained from commercial sources. The activated polyethylene glycol conjugates listed in the left hand column of the Table BB below can readily be prepared and their molecular weight determined by one skilled in the art view of known methods such as described in European Patent Applications EP 0 236 987, EP 0 510 356 and EP 0 809 996 as well as U.S. Patent No. 5,642,575. to obtain the compounds of formula I or a pharmaceutical acceptable salt thereof wherein the R is the moiety listed in the right hand column of the Table BB below.

30

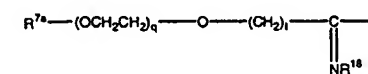
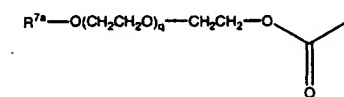
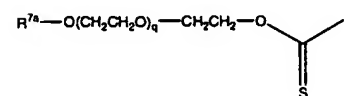
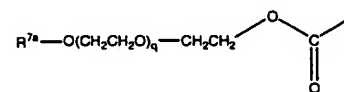
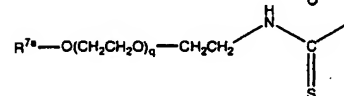
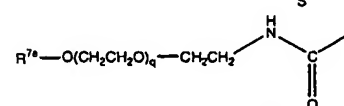
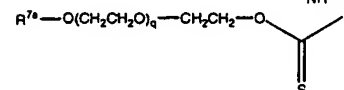
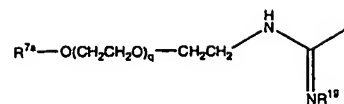
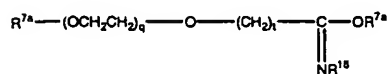
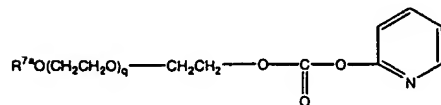
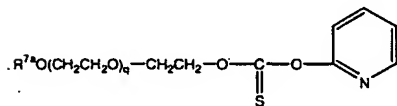
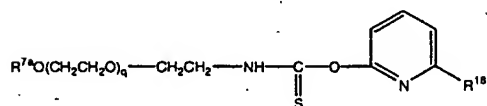
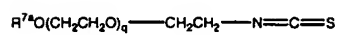
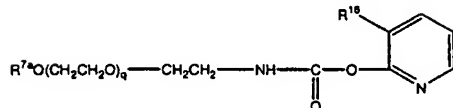
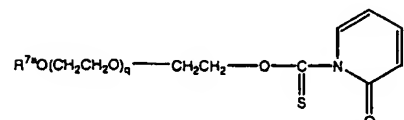
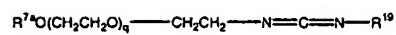


TABLE BB

## COLUMN A

## COLUMN B

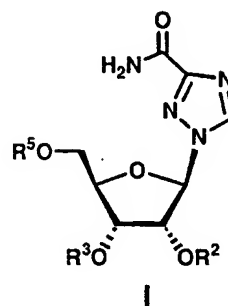
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CLAIMS:

1. A compound represented by formula I



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wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^2$ ,  $R^3$  or  $R^5$  is H,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$  and wherein at least one of  $R^2$ ,  $R^3$  or  $R^5$  is not H; wherein  $R^6$  is H, alkyl, alkanoyl, aryl, heterocyclic, cycloalkyl,  $NR^{7a}R^{7b}$ , alkenyl, or alkynyl; or  $R^6$  is alkyl, alkanoyl, alkenyl or alkynyl substituted by halo, phenyl, cycloalkyl,  $NR^{7a}R^{7b}$ , hydroxy, or alkoxy;

or  $R^6$  is aryl substituted by phenyl; halo, CN,  $NO_2$ , OH,  $R^{18}$ ,  $CF_3$ , SH,  $SR^{7a}$ ,  $SOR^{7a}$ ,  $SO_2R^{7a}$ ;  $NR^{7a}R^{7b}$ ,  $CO_2H$ ,  $CO_2^-$ ,  $OR^{7a}$ ,  $O^-M^+$  or  $S^-M^+$  wherein  $M^+$  is an alkali metal,

20

W is O,  $NR^{18}$  or S;

$R^{7a}$  is H, alkyl, alkanoyl, or aryl; or  $R^{7a}$  is alkyl, alkanoyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

25

and  $R^{7b}$  is H, alkyl or aryl or  $R^{7b}$  is alkyl or aryl substituted by phenyl halo, CN,  $NO_2$ , OH,  $CO_2H$ , or alkoxy;

or  $R^{7a}$  and  $R^{7b}$  taken together with N and one of  $CHR^{7a}$ ,  $NR^{7a}$ , O, S, SO or  $SO_2$  form a five-, six- or seven- membered ring;



$R^{17}$  is H,  $OR^{7a}$ ,  $NR^{7a}R^{7b}$ ,  $R^6-(W)_x-CO-$ ,  $R^6-(W)_x-CS-$ ,  $R^6-(W)_x-C=NR^{18}-$ ,  $(HO)_2PO-$ ,  $R^6-(W)_x-PO(OH)-$  or  $HO-SO_2-$ ;

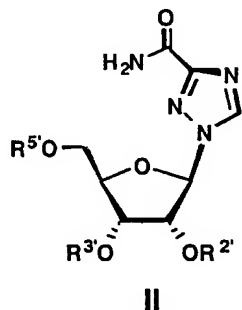
$R^{18}$  is H, alkanoyl or alkyl;

and  $x = 0$  or  $1$ ;

5

or a pharmaceutically acceptable salt thereof.

2. A compound represented by formula II

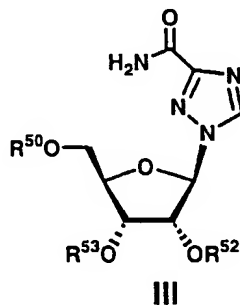


10

wherein at least one of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a straight or branched chain polyalkylene oxide polymer conjugate, and wherein at least one of the remaining of  $R^{2'}$ ,  $R^{3'}$  or  $R^{5'}$  is a natural or unnatural  $\alpha$ -amino acid residue; or a pharmaceutically acceptable salt thereof.

15

3. A compound represented by formula III

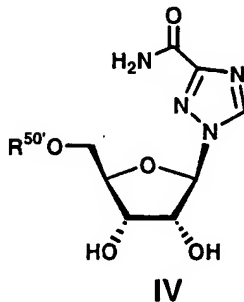


wherein at least one of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  is a straight or branched chain polyalkylene oxide polymer conjugate; and the remaining two of  $R^{50}$ ,  $R^{52}$ ,  $R^{53}$  are independently H or a straight or branched chain polyalkylene oxide polymer conjugate, or a pharmaceutically acceptable salt thereof

20



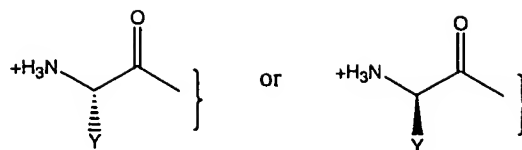
4. A compound represented by the formula IV



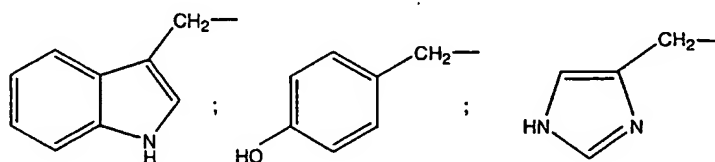
wherein R<sup>50'</sup> is a straight or branched chain polyalkylene oxide polymer conjugate; or a pharmaceutically acceptable salt thereof

5. The compound of claim 1 wherein R<sup>2</sup> or R<sup>3</sup> is a natural or unnatural  $\alpha$ -amino acid residue or the compound of claim 2 wherein R<sup>2'</sup> or R<sup>3'</sup> is a natural or unnatural  $\alpha$ -amino acid residue; the natural or unnatural  $\alpha$ -amino acid residue being represented by the formula:



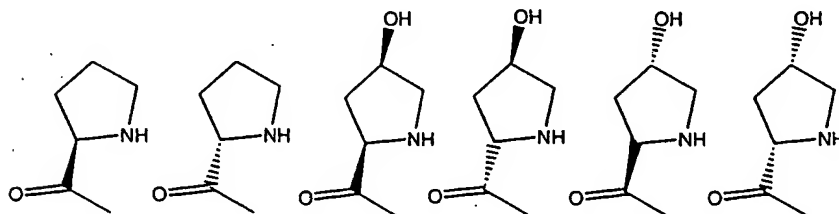


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;



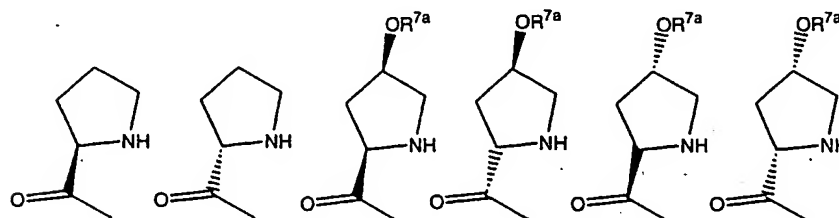
or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)- or a pharmaceutically acceptable salt thereof;

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.

or Y taken together with the  $\alpha$  carbon and N form



or a pharmaceutically acceptable salt thereof.

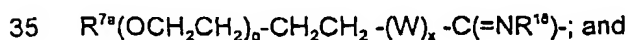
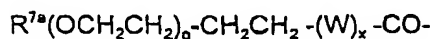
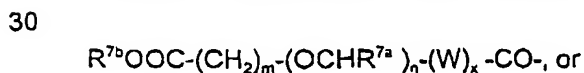
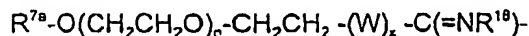
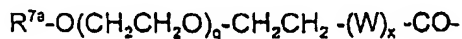
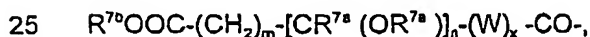
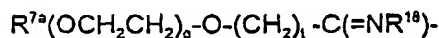
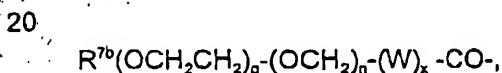
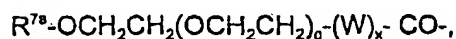


6. The use of a compound of any preceding claim for the manufacture of a pharmaceutical composition for treating patients having chronic hepatitis C infection to eradicate detectable HCV-RNA

5 7 The use of a compound of any preceding claim and a interferon-alpha for the manufacture of a pharmaceutical composition for treating patients having chronic hepatitis C infection to eradicate detectable HCV-RNA ;  
or a pharmaceutically acceptable salt thereof.

10 8. The compound, pharmaceutical composition or use of any preceding claim (a) wherein  $R^2 = R^3 = H$ . or wherein  $R^2$  or  $R^3 = H$ ; or (b) wherein  $R^2 = R^5 = H$ . or wherein  $R^2$  or  $R^5 = H$ ; or (c). wherein  $R^3 = R^5 = H$ . or wherein  $R^3$  or  $R^5 = H$

15 9 The compound, pharmaceutical composition or use of any preceding claim wherein (a) at least one of  $R^2$ ,  $R^3$  or  $R^5$  in claim 1 or (b) at least one of  $R^2$ ,  $R^3$  or  $R^5$  in claim 2; or (c) at least one of  $R^{52}$ ,  $R^{53}$  or  $R^{50}$  in claim 3; or (d)  $R^{50}$  in claim 4 is one of  
is one of





$W = -O-$  or  $-NR^{18}-$ ; and  $R^{18} = H$ ;

$m = 0$  to  $100$ ;  $n = 0$  to  $6000$ ;  $t = 1$  to  $4$ ; and  $q = 1$  to  $5000$ .

- 5 10. The compound, pharmaceutical composition or use of any preceeding claim wherein  $R^2 = R^3 = H$ ; or wherein  $R^2 = R^3 = H$ ; and  $R^5$  or  $R^{5'}$  or  $R^{50}$  or  $R^{50'}$  is one of  $R^{7a}-OCH_2CH_2(OCH_2CH_2)_q-(W)_x-CO-$ ;

$R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-(W)_x-CO-$ ,

10

$R^{7a}-(OCH_2CH_2)_q-O-(CH_2)_t-C(=NR^{18})-$

$R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-CO-$

15

$R^{7a}-O(CH_2CH_2O)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$

$R^{7b}(OCH_2CH_2)_q-(OCH_2)_n-(W)_x-CO-$ ,

$R^{7b}OOC-(CH_2)_m-[CR^{7a}(OR^{7a})]_n-(W)_x-CO-$ ,

20

$R^{7b}OOC-(CH_2)_m-(OCHR^{7a})_n-(W)_x-CO-$  or

$R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-CO-$

25

$R^{7a}(OCH_2CH_2)_q-CH_2CH_2-(W)_x-C(=NR^{18})-$

$W = -O-$  or  $-NR^{18}-$ ; and  $R^{18} = H$ ;

and

30

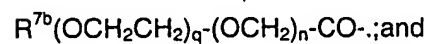
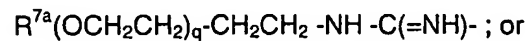
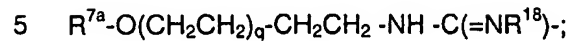
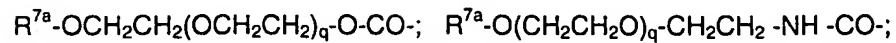
$m = 0$  to  $100$ ;  $n = 0$  to  $6000$ ;  $q = 1$  to  $5000$ ;  $t = 1$  to  $4$ ; and  $x = 0$  or  $1$ .

11. The compound, pharmaceutical composition or use of any preceeding claim wherein  $R^2 = R^3 = H$  or wherein  $R^2 = R^3 = H$  and  $R^5$  or  $R^{5'}$  or  $R^{50}$  or  $R^{50'}$  is one of

35

$R^{7b}-OOC-CH_2(OCH_2CH_2)_qOCH_2CO-$ ,  $R^{7a}-OCH_2CH_2(OCH_2CH_2)_qOCH_2CO-$





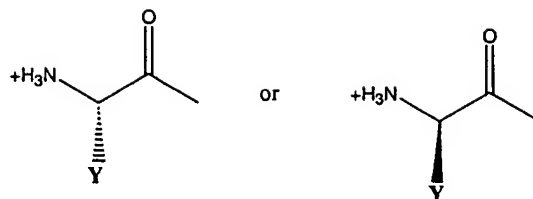
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$n = 0$  to  $6000$ ; and  $q = 1$  to  $5000$ .

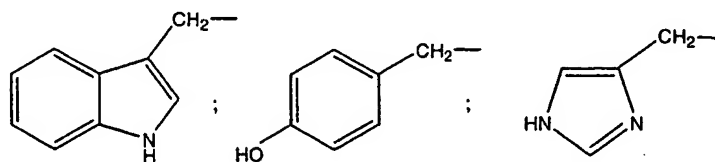
12. The compound, pharmaceutical composition or use of any preceding claim  
 (a) wherein  $R^5$  is a straight or branched chain polyalkylene oxide polymer conjugate,  
 15 and  $R^3$  or  $R^2$  or is a natural or unnatural  $\alpha$ -amino acid moiety or (b) wherein  $R^5$  is a  
 straight or branched chain polyalkylene oxide polymer conjugate, and  $R^3$  or  $R^2$  is a  
 natural or unnatural  $\alpha$ -amino acid residue and wherein the natural or unnatural  $\alpha$ -  
 amino acid residue is selected from



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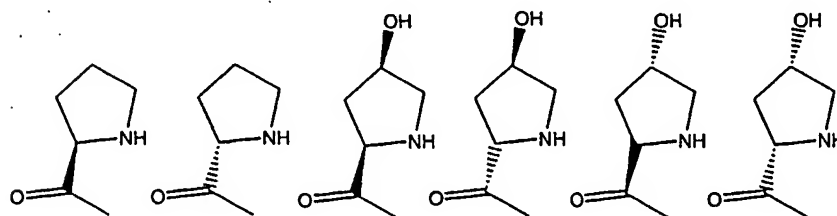


wherein Y = H, CH<sub>3</sub>; CH<sub>3</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-; Me<sub>2</sub>CH-; Me<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-; CH<sub>3</sub>CH<sub>2</sub>CH(Me)-  
PhCH<sub>2</sub>-; HOOCCH<sub>2</sub>CH<sub>2</sub>-; HSCH<sub>2</sub>-; HOOCCH<sub>2</sub>-; MeSCH<sub>2</sub>CH<sub>2</sub>-; HOCH<sub>2</sub>-;

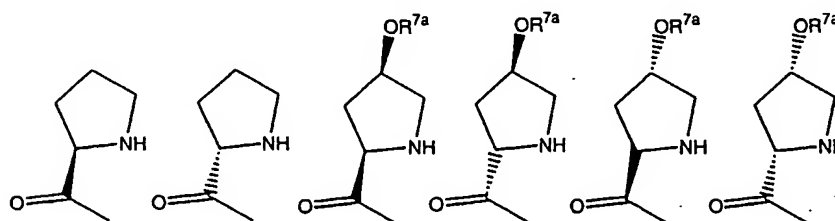


or Y is H<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>- or CH<sub>3</sub>CH(OH)- or a pharmaceutically acceptable salt thereof;

or Y taken together with the a carbon and N form



or form



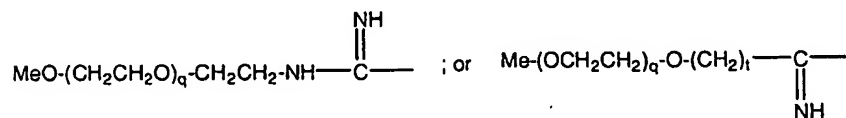
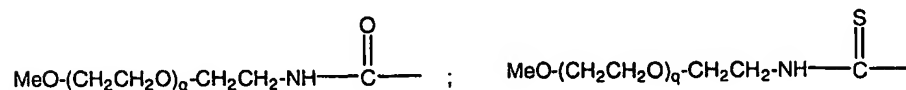
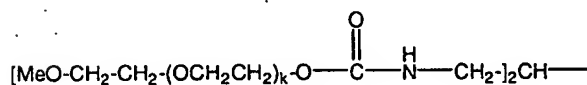
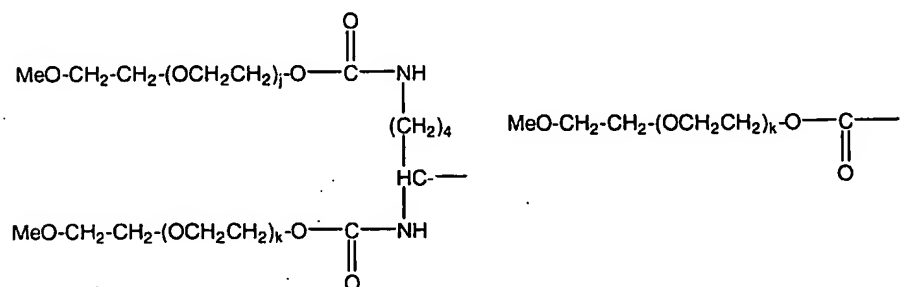
wherein R<sup>7a</sup> is as described herein above;

or a pharmaceutically acceptable salt thereof.



13 The compound of claim 3 or 4 wherein the straight or branched chain polyalkylene oxide polymer conjugate is a straight or branched chain polyethylene oxide polymer conjugate.

14. The compound of claim 13 wherein the straight or branched chain polyethylene oxide polymer conjugates are represented by the formulas ,



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or a pharmaceutically acceptable salt thereof.



15. The method of treating a patient with a susceptible viral infection which comprises administering to said patient an effective amount of a compound of any preceding claim

5 16. The method of treating a patient infected with chronic hepatitis C which comprises administering to said patient an effective amount of a compound of any preceding claim in association with an effective amount of an interferon alfa for a time sufficient to eradicate detectable HCV-RNA levels,

10 17. The use of any preceding claim, wherein the amount of a compound of any preceding claim administered is from about 1 to about 100 mg per kilogram per day.

15 18. The use of any preceding claim, wherein the interferon-alpha administered is selected from interferon alpha-2a, interferon alpha-2b, a consensus interferon, a purified interferon alpha product or a pegylated interferon-alpha.

19. A pharmaceutical composition comprising a compound of any preceding claim and a pharmaceutically acceptable carrier.

20 20. The use of any preceding claim, wherein the interferon-alpha is selected from interferon alpha-2a, interferon alpha-2b, or a purified interferon alpha product and the amount of interferon-alpha administered is from 2 to 10 million IU per week on a weekly, TIW, QOD or daily basis, and preferably the amount of interferon-alpha administered is 3 million IU TIW.

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 99/21450

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07H19/056 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 96 04924 A (CYTRX CORP) 22 February 1996 (1996-02-22) claims 10,20	1-20
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	-/-	

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

2 March 2000

Date of mailing of the international search report

10/03/2000

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## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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